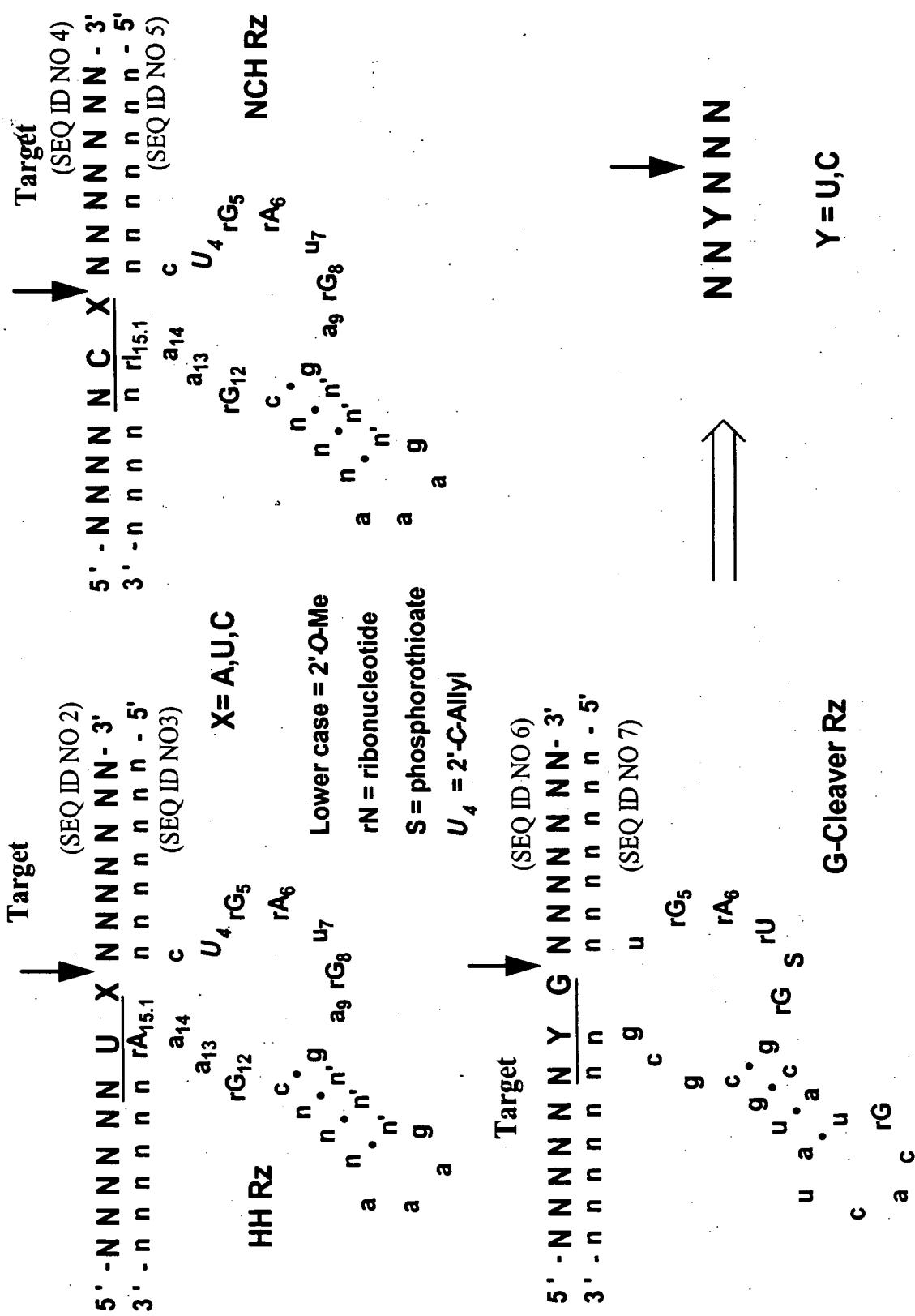
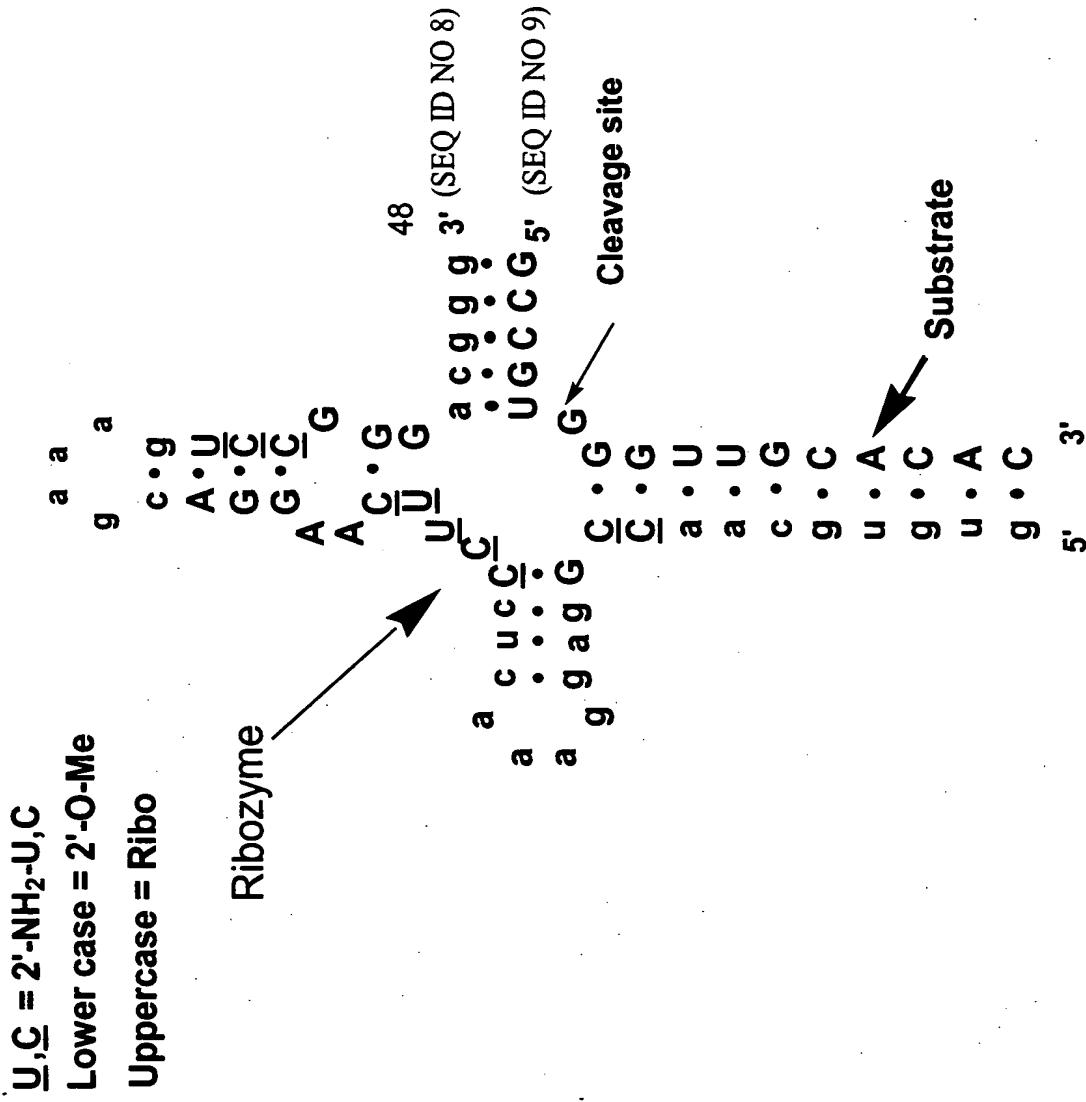


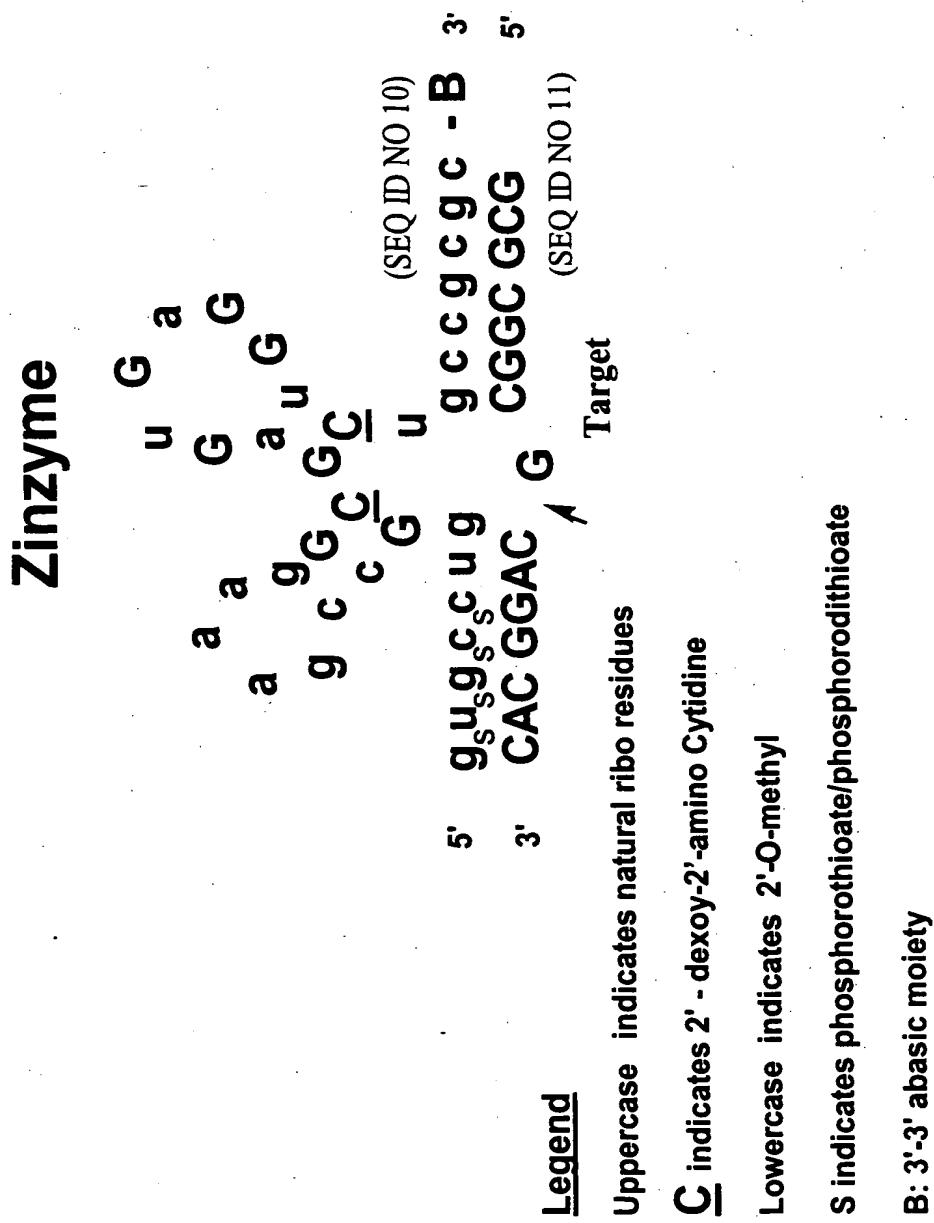
**Figure 1: Examples of Nucleic Acid Stable Ribozyme Motifs**



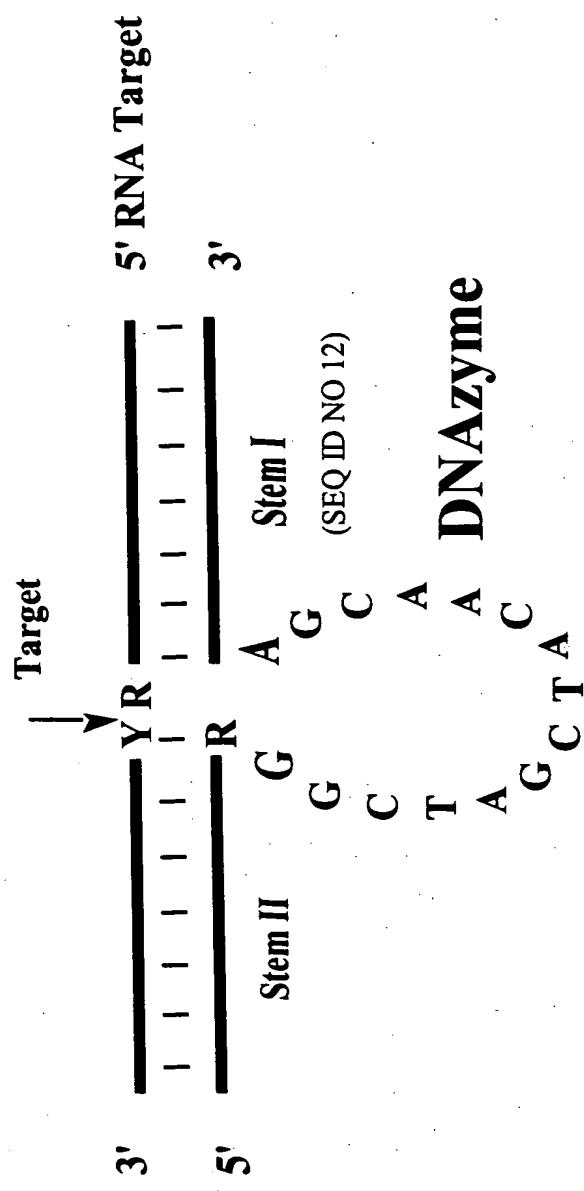
**Figure 2: 2'-O-Me substituted Amberzyme Enzymatic Nucleic Acid Motif**



**Figure 3: Stabilized Zinzyme Ribozyme Motif**



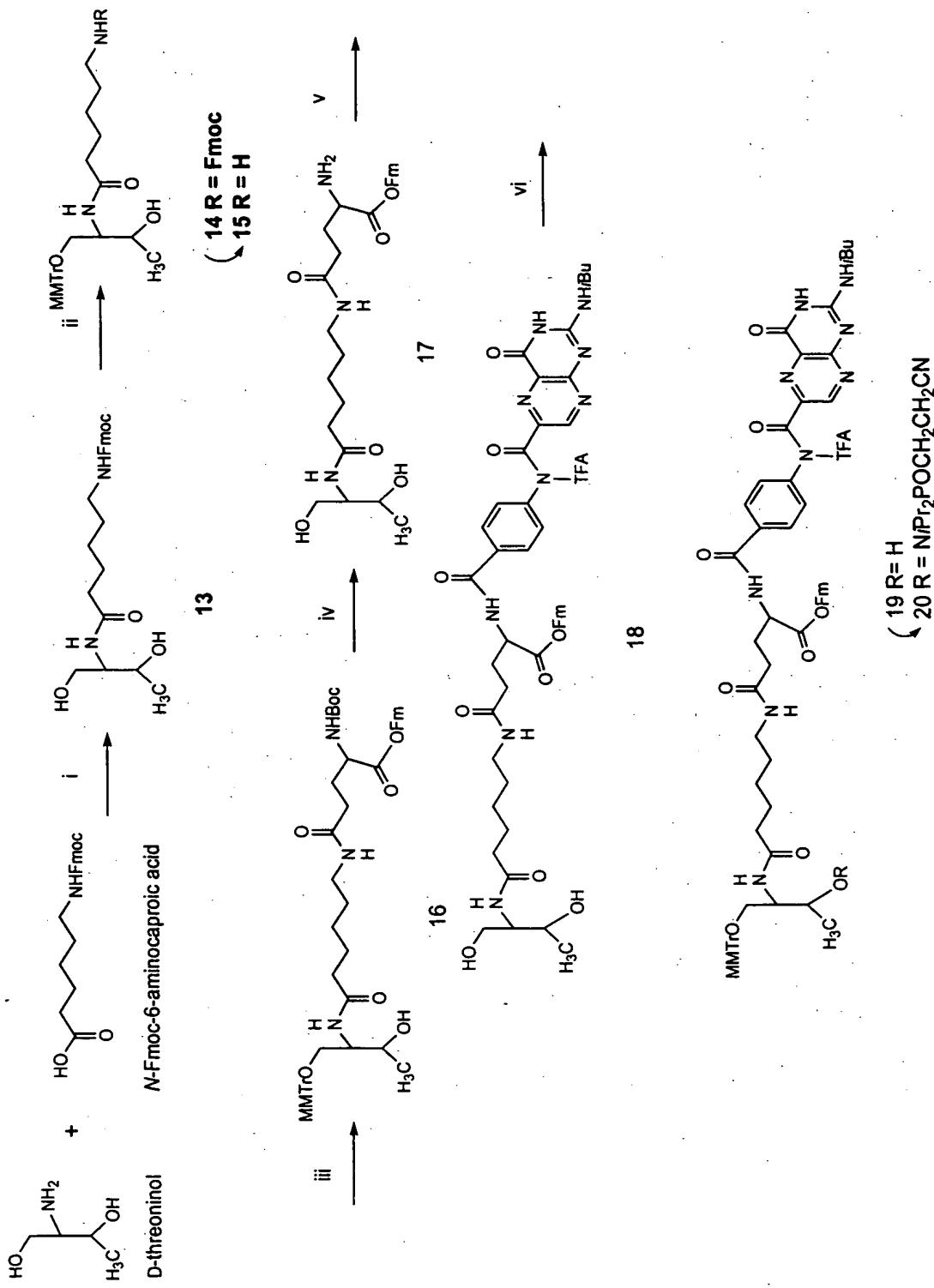
**Figure 4: DNAzyme Motif**



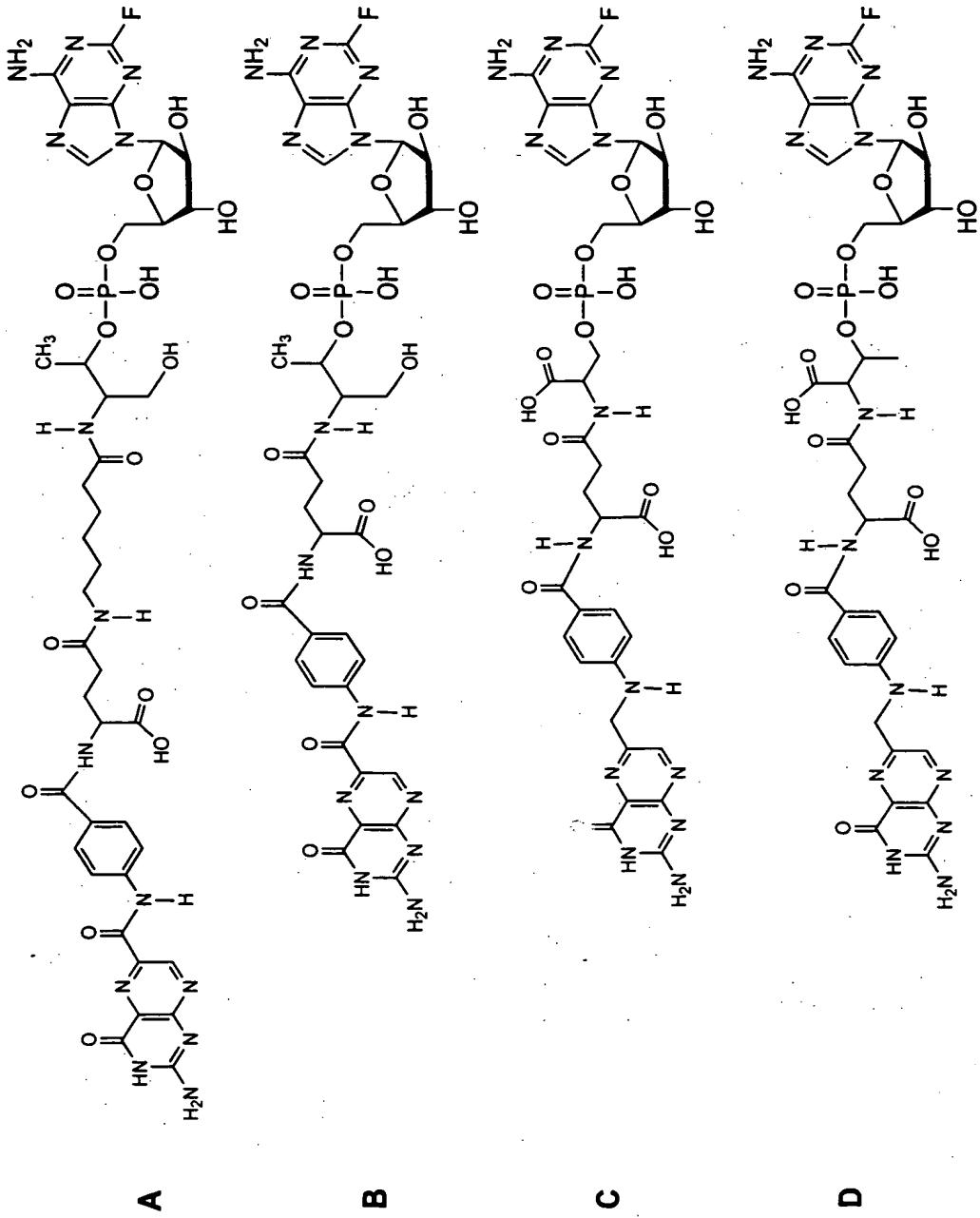
**Legend**

Y = U or C  
R = A or G

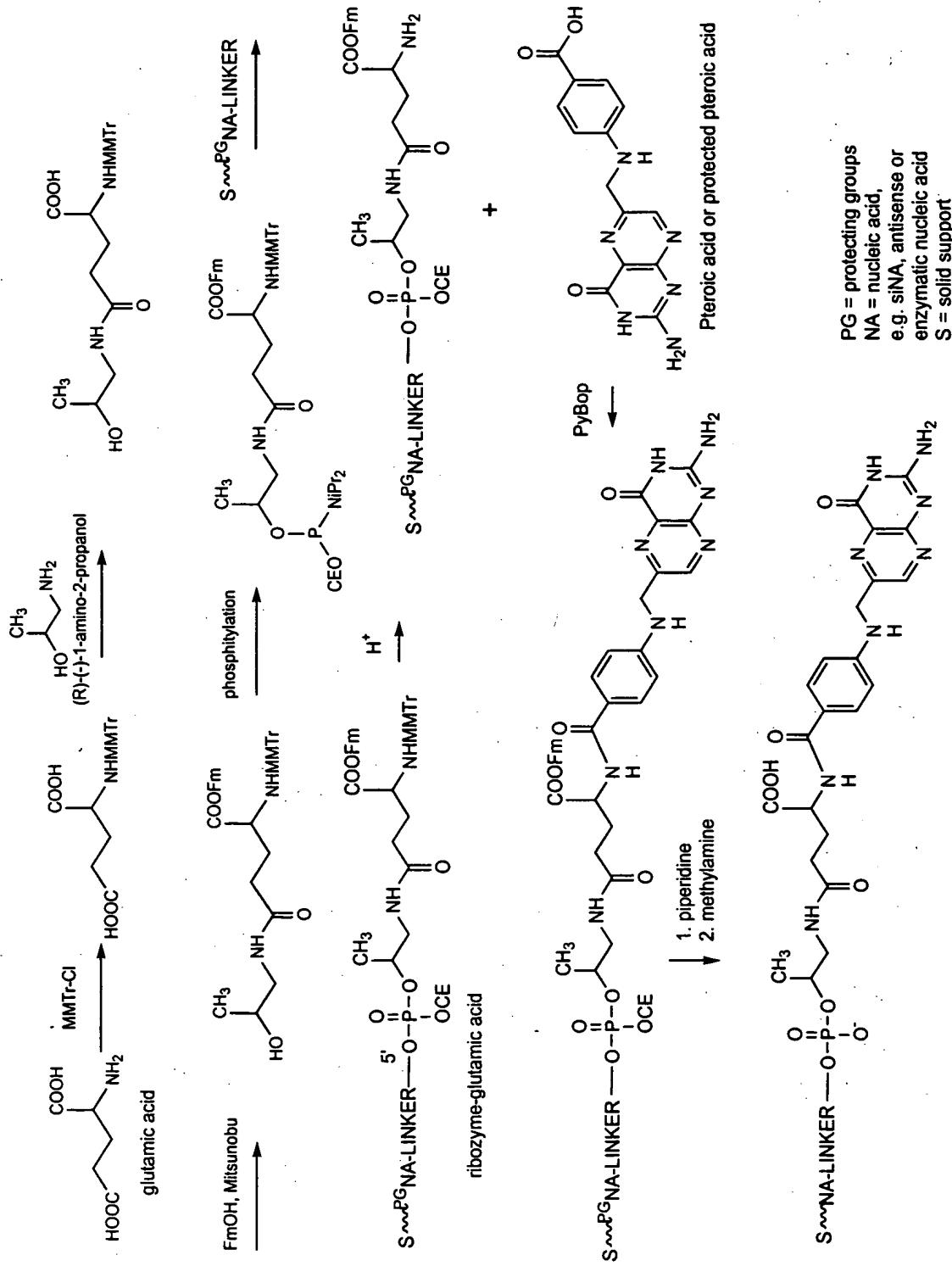
**Figure 5: Synthesis of Folate Linked phosphoramidite**



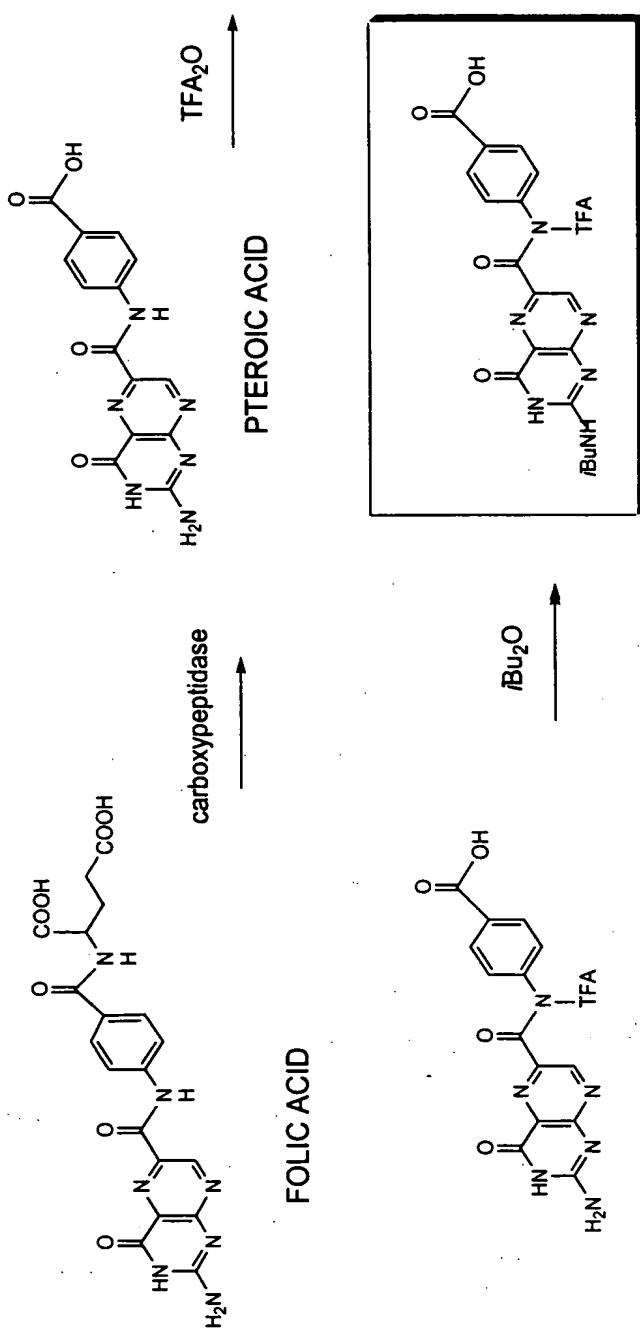
**Figure 6: Fludarabine-Folate conjugates**



**Figure 7: Solid Phase Post-synthetic conjugation of pteroic acid**

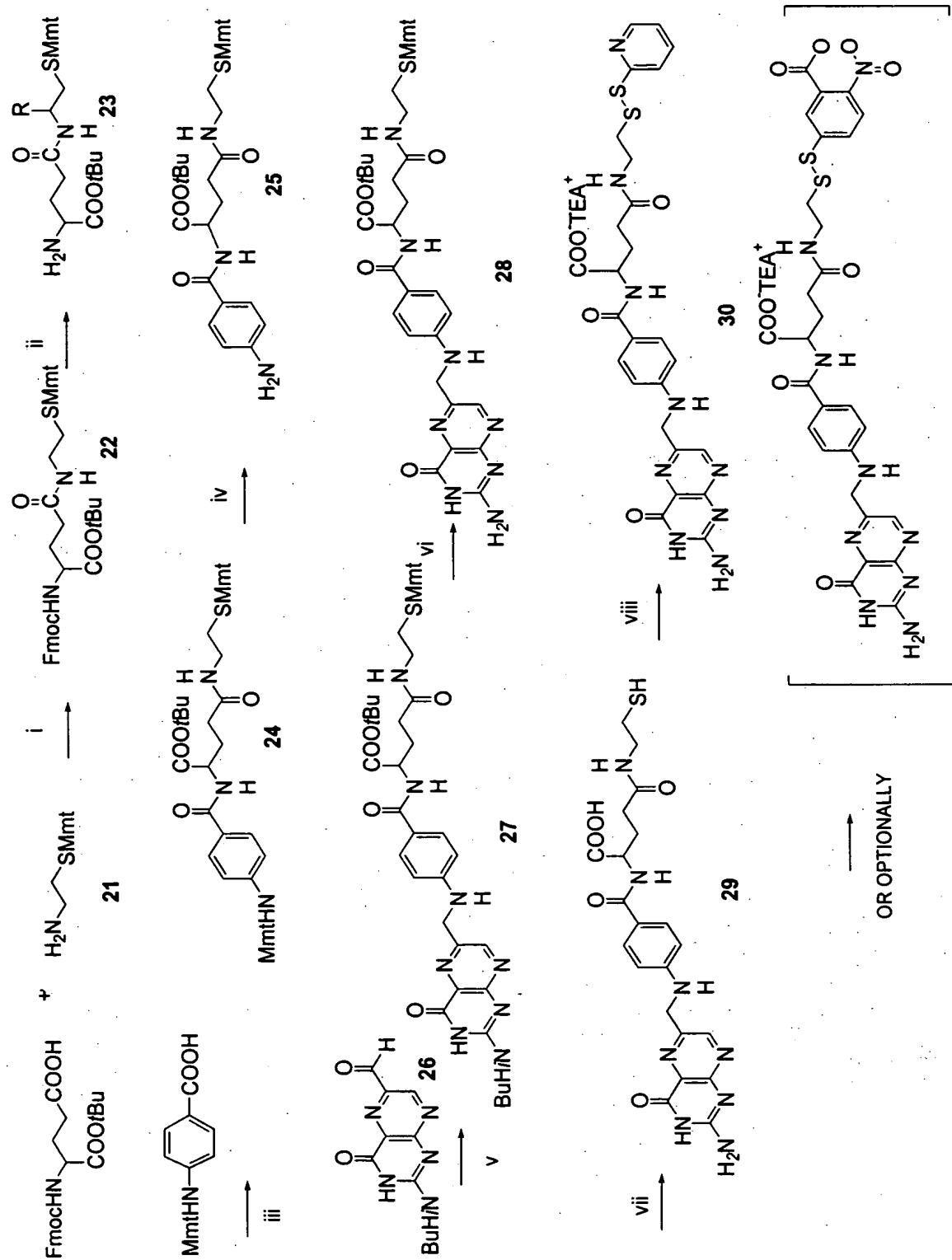


**Figure 8: Chemo-enzymatic synthesis of pteroic acid synthon**

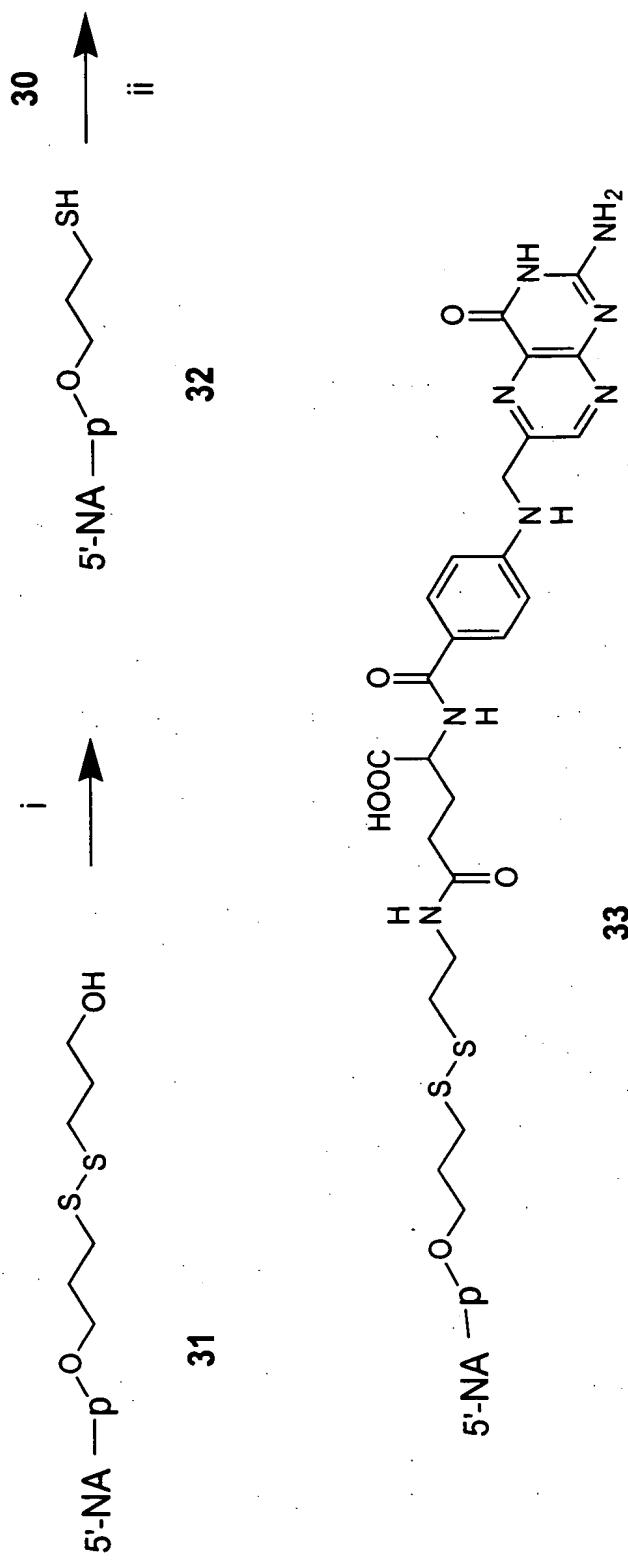


**Figure 9**

Atty Dkt No. 02-312-G; 600.041  
Title: Conjugates and Compositions...  
Serial No.: not yet known; Vargeese et al.  
Sheet 9 of 51

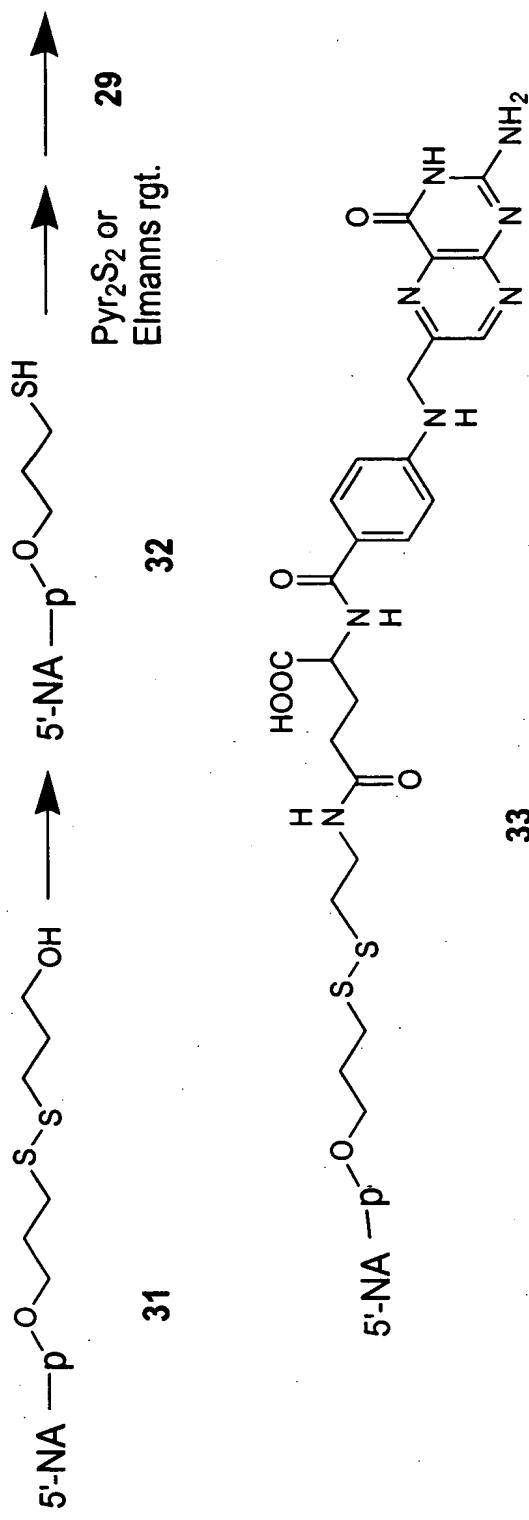


**Figure 10**



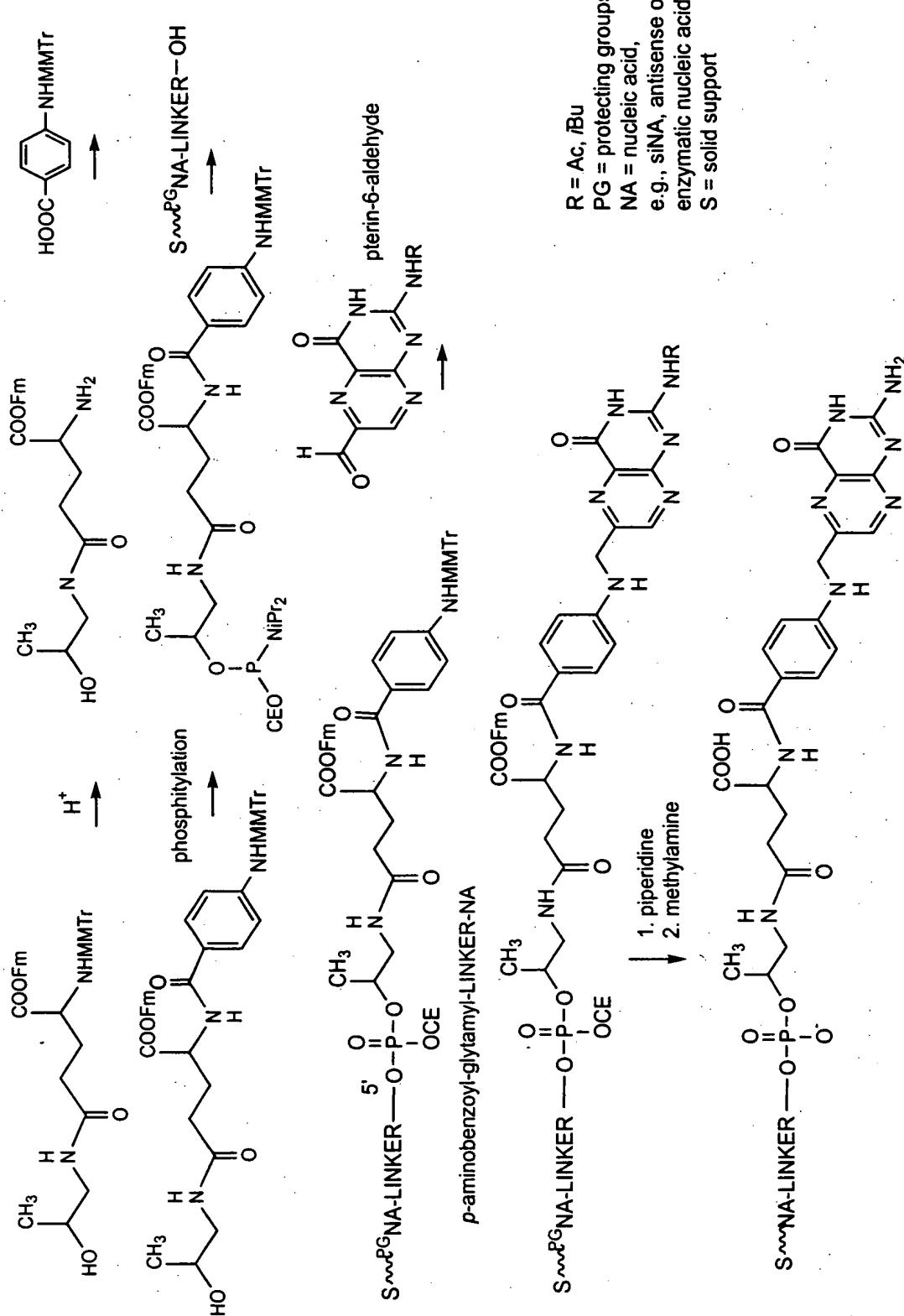
NA = Nucleic Acid, such as siNA, antisense, or enzymatic nucleic acid  
p = phosphorous moiety

**Figure 11**

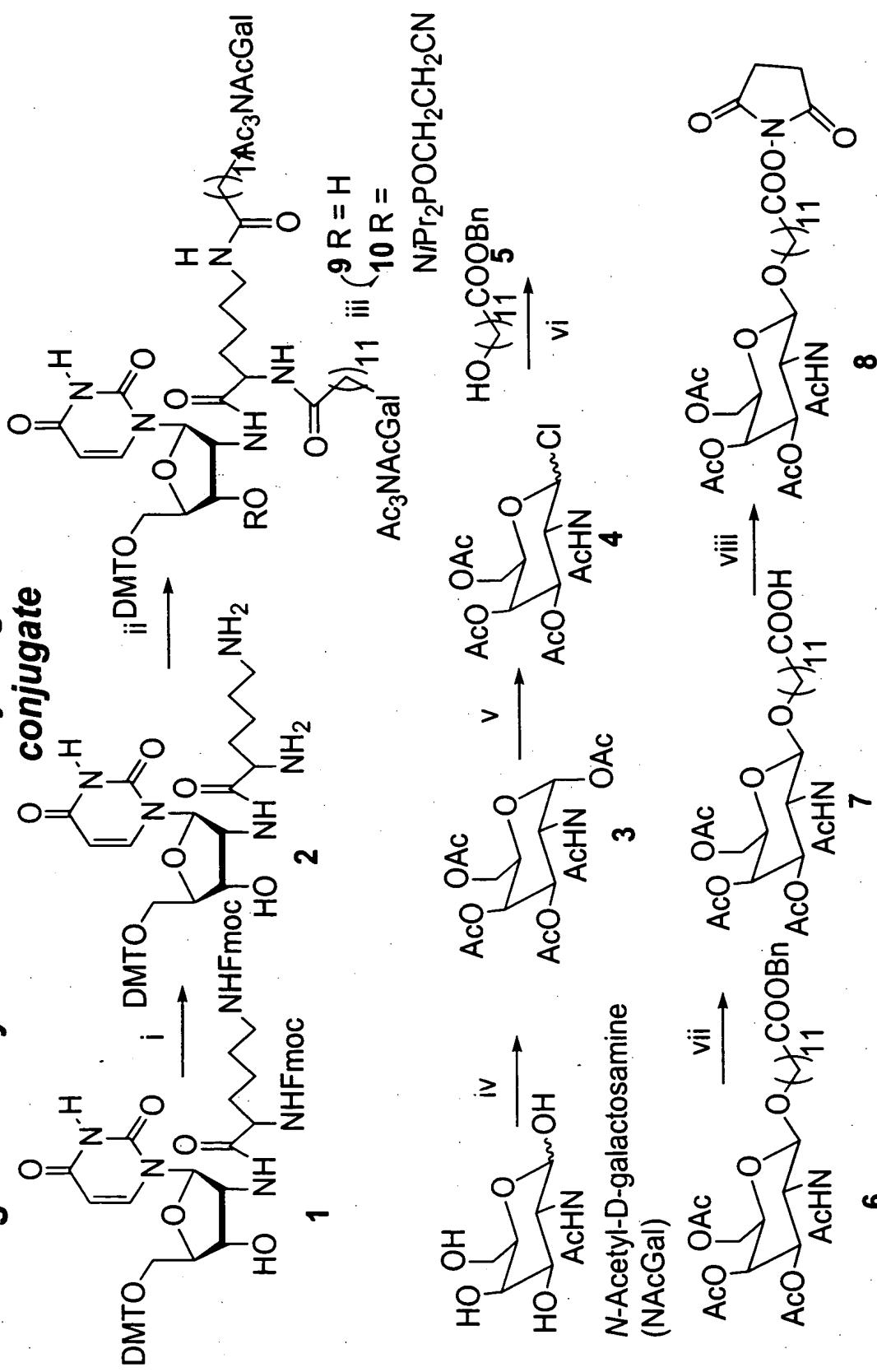


NA = Nucleic Acid, such as siNA, antisense, or enzymatic nucleic acid  
p = phosphorous moiety

**Figure 12: Solid Phase Post-synthetic conjugation of pteroic acid**

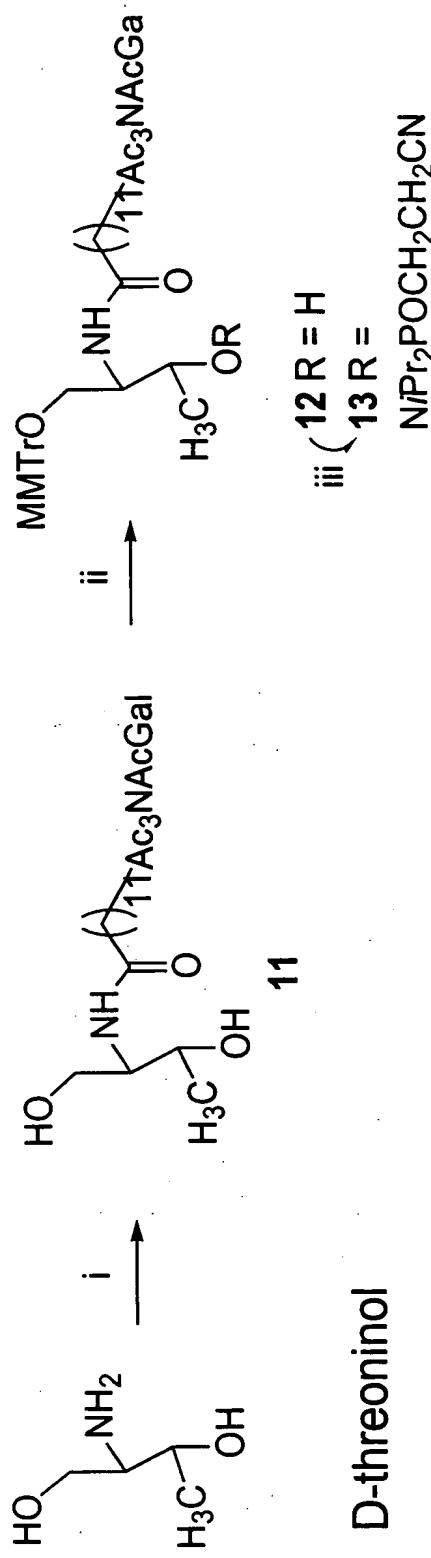


**Figure 13: Synthesis of *N*-acetyl-D-galactosamine-2'-aminouridine conjugate**



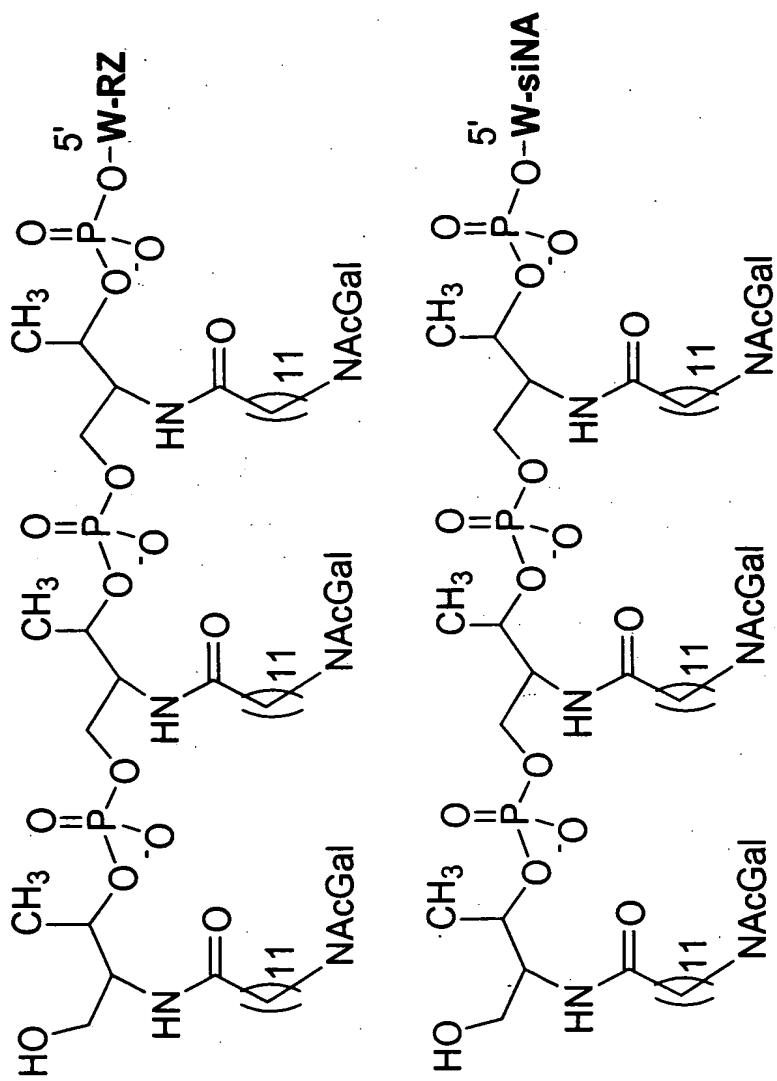
Reagents and Conditions: (i) diethylamine, DMF, (ii) **8**, diisopropylethylamine, DMF, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, (iv) Ac<sub>2</sub>O, TEA, CH<sub>3</sub>CN, (v) HCl, Ac<sub>2</sub>O, (vi) Hg(CN)<sub>2</sub>, MS 4A, CH<sub>3</sub>NO<sub>2</sub>-toluene 1:1, (vii) H<sub>2</sub>, 5% Pd-C, ethanol, (viii) N-hydroxysuccinimide, DCC, THF.

**Figure 14:** Synthesis of N-acetyl-D-galactosamine-D-threoninol conjugate



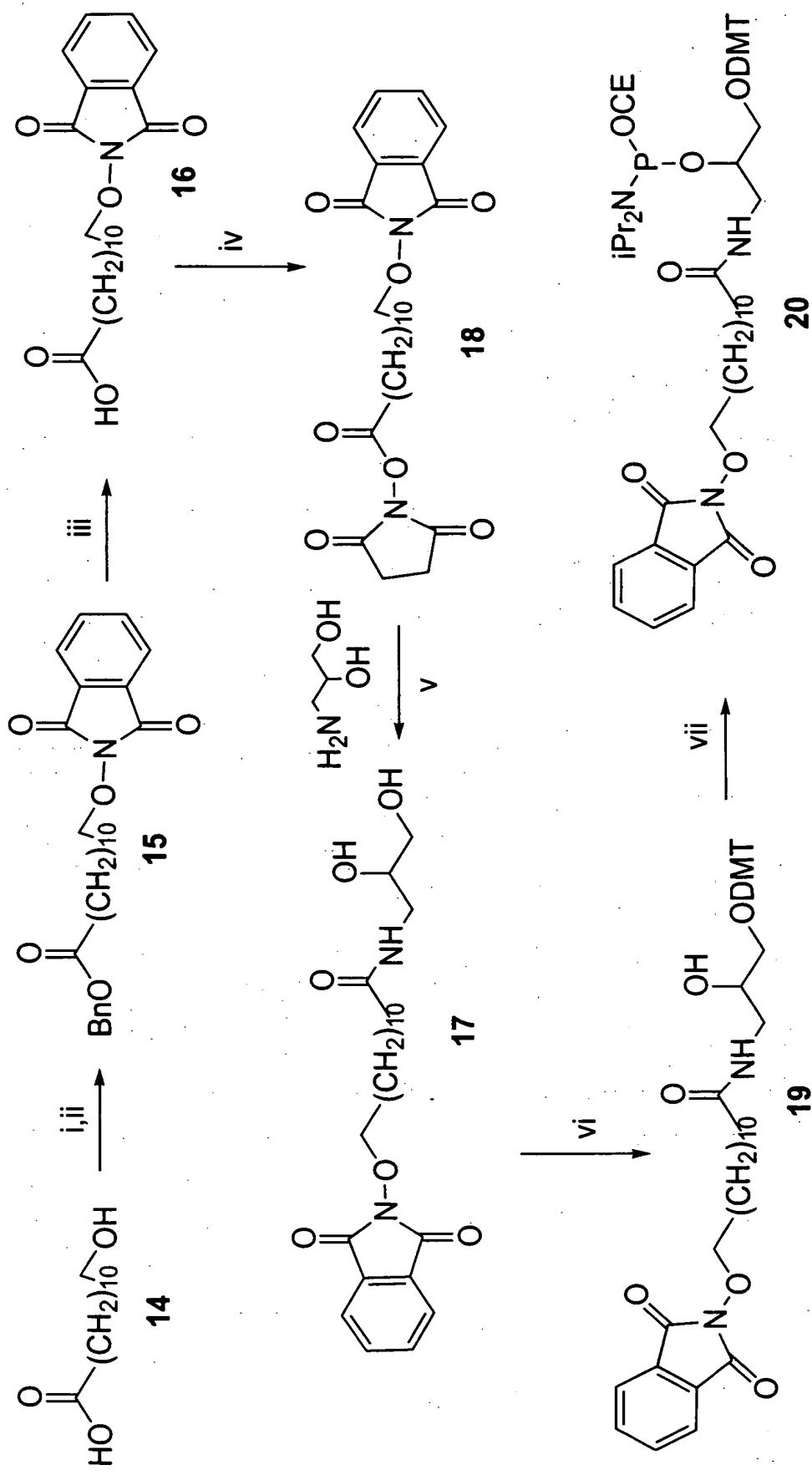
Reagents and Conditions: (i) 7, DCC, *N*-hydroxysuccinimide, (ii) MMTr-Cl, pyridine, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>.

**Figure 15: Conjugation of targeting ligands to the 5'-end of a Ribozyme or siNA molecule**

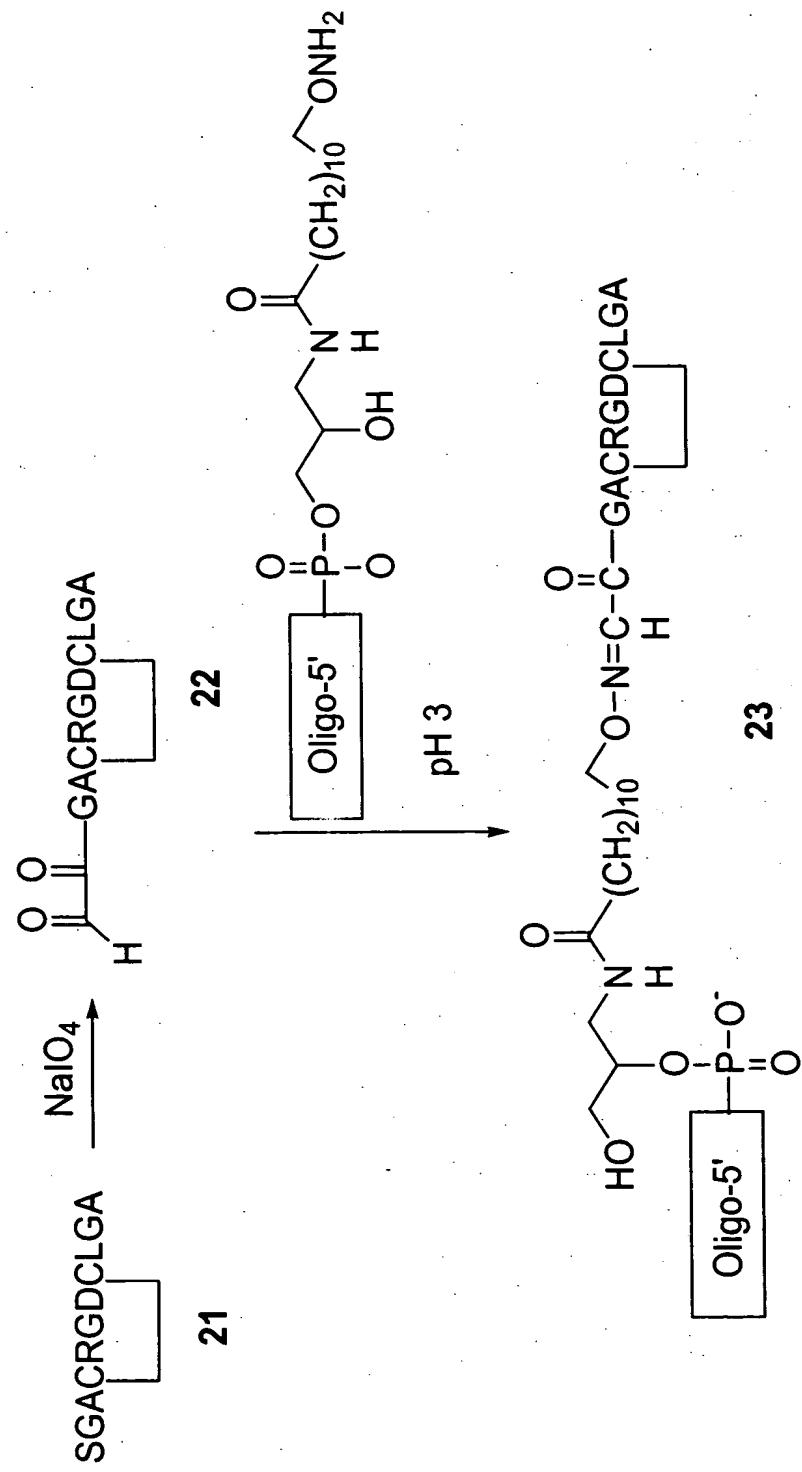


*N*-acetyl-D-galactosamine conjugate

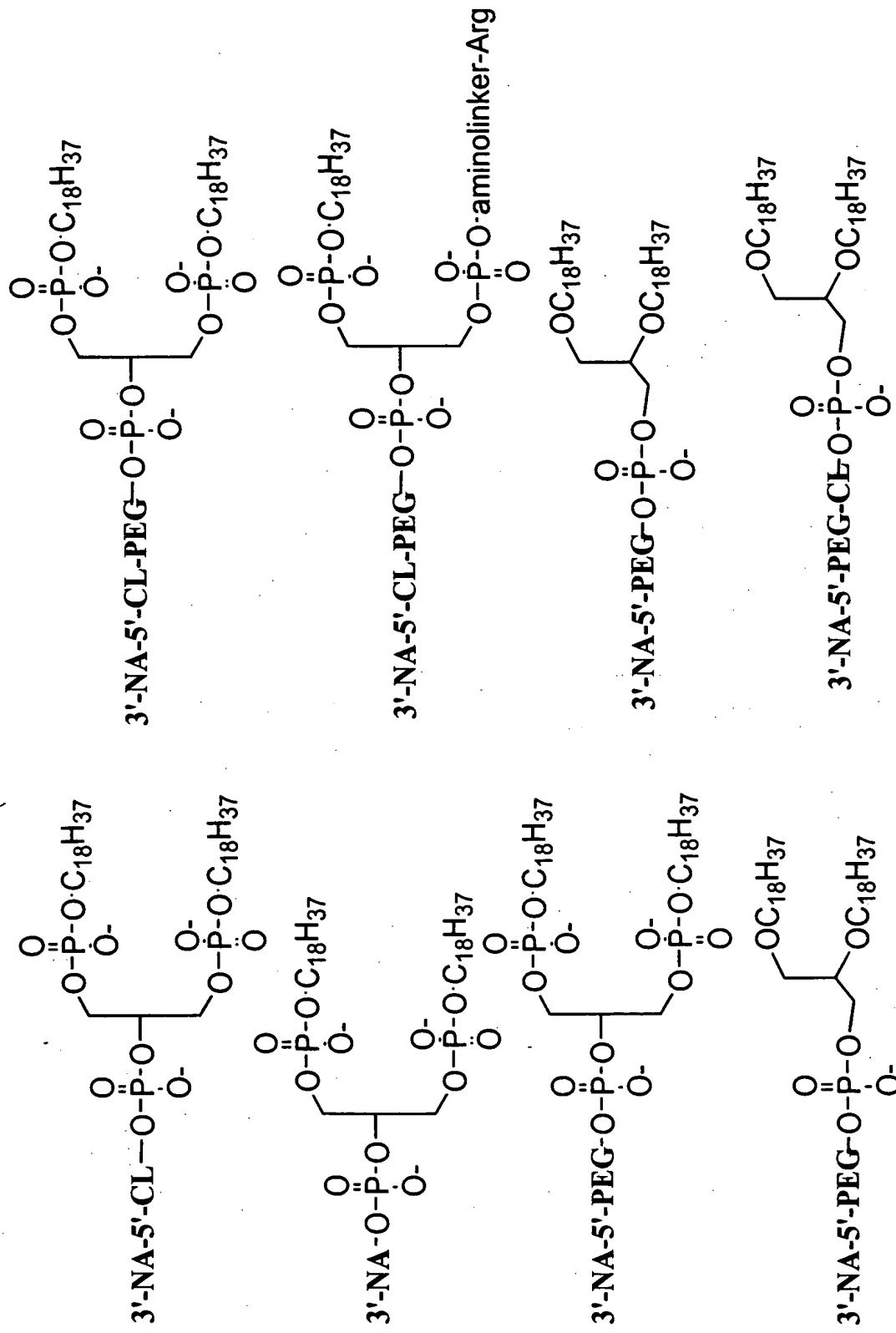
**Figure 16: Synthesis of dodecanoic acid linker**



**Figure 17: Oxime linked Nucleic Acid/Peptide Conjugate**



**Figure 18: Nucleic Acid/Phospholipid Conjugates**

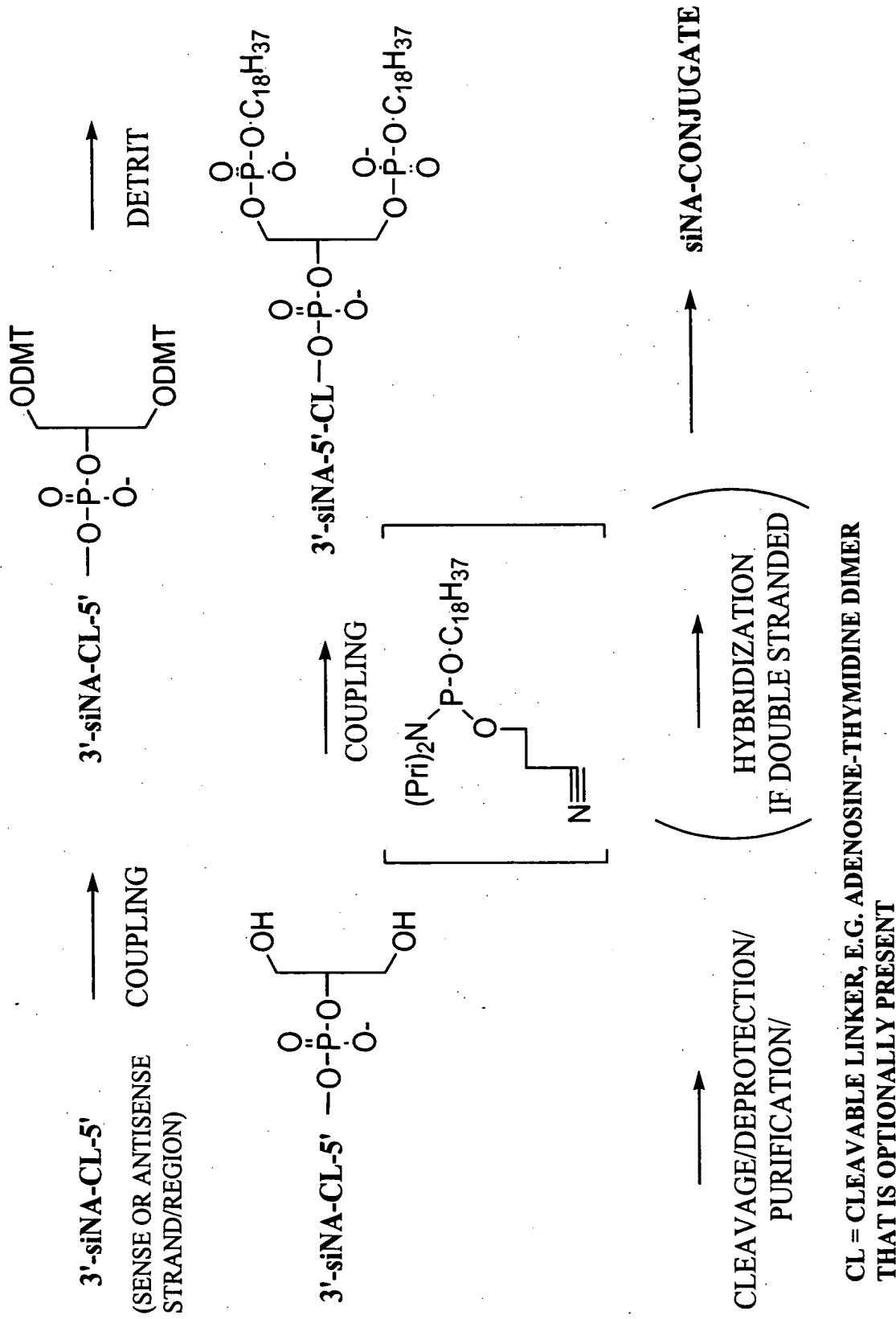


PEG=polyethylene glycol

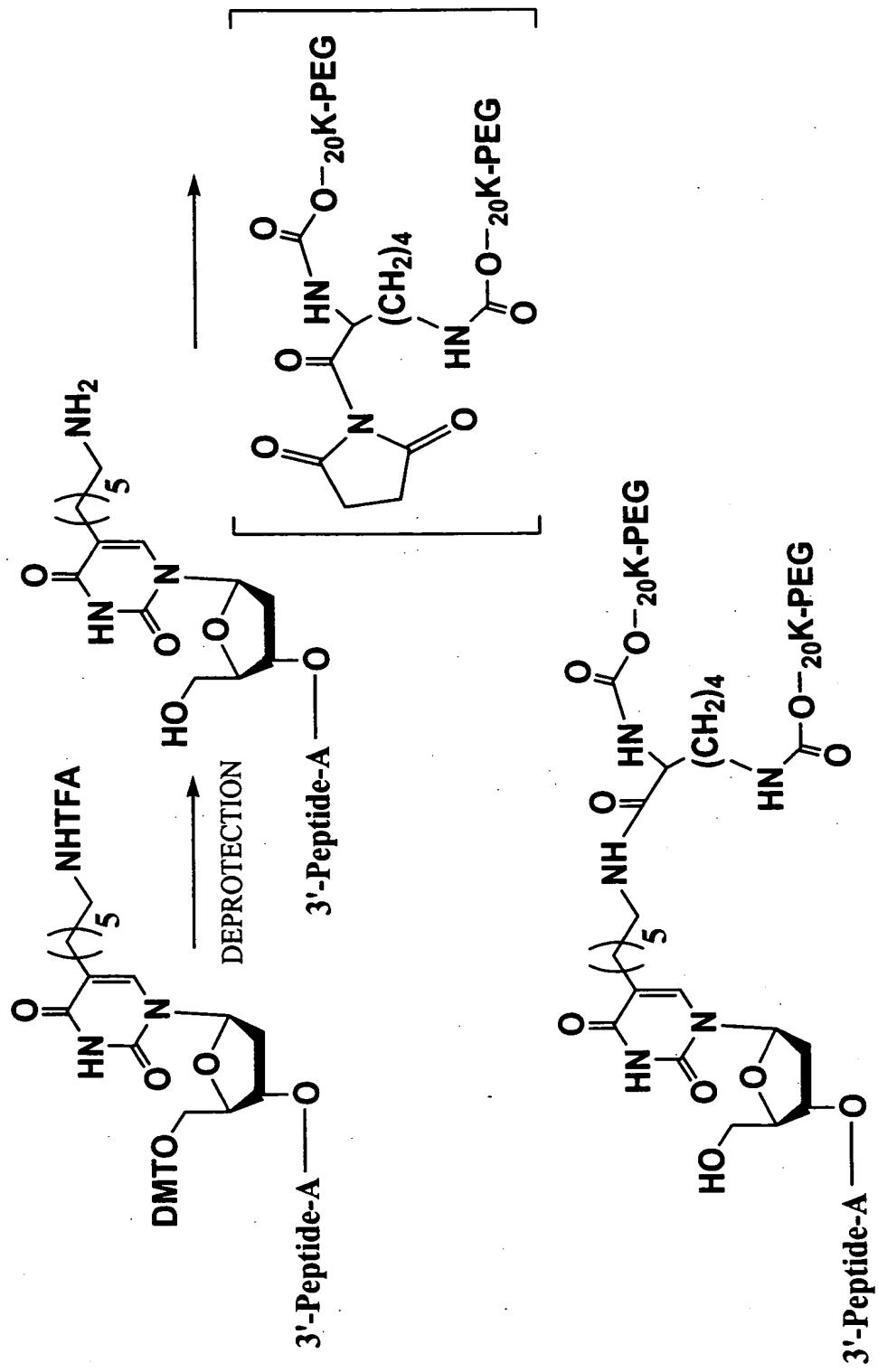
CL=cleavable linker (e.g. A-dT, C-dT)

NA=Nucleic Acid Molecule such as siNA, antisense, or enzymatic nucleic acid

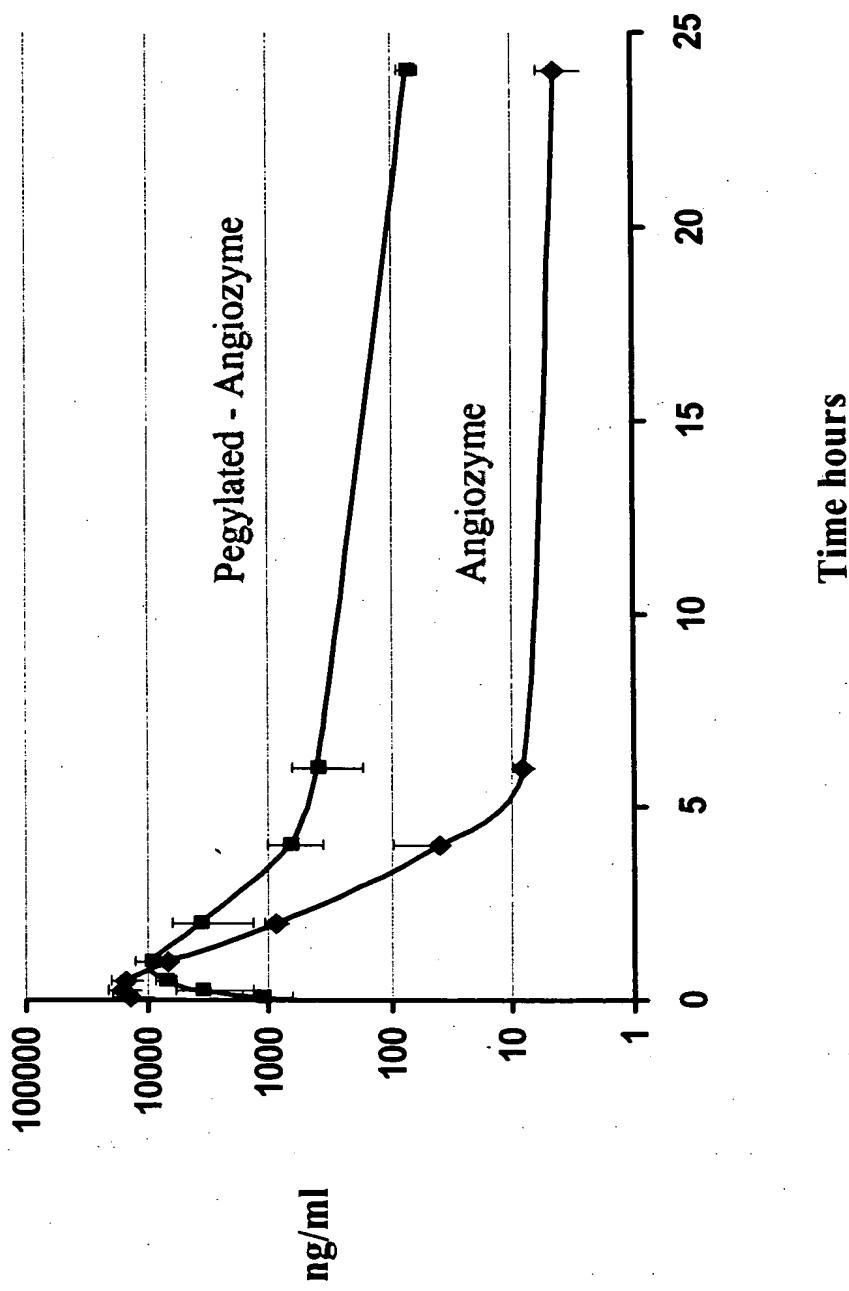
*Figure 19: siNA Phospholipid Conjugate*



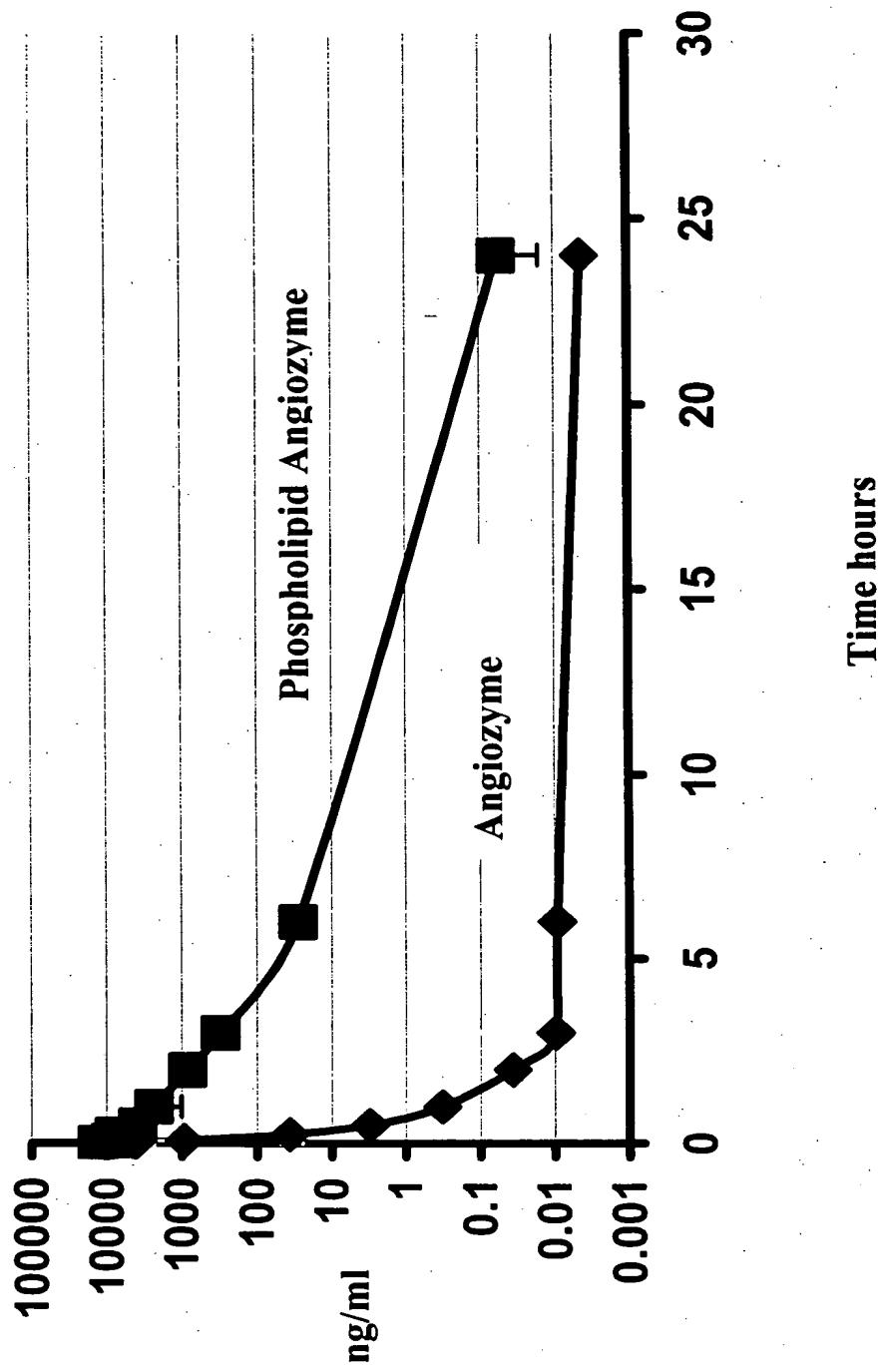
*Figure 20: Peptide PEG Conjugate*



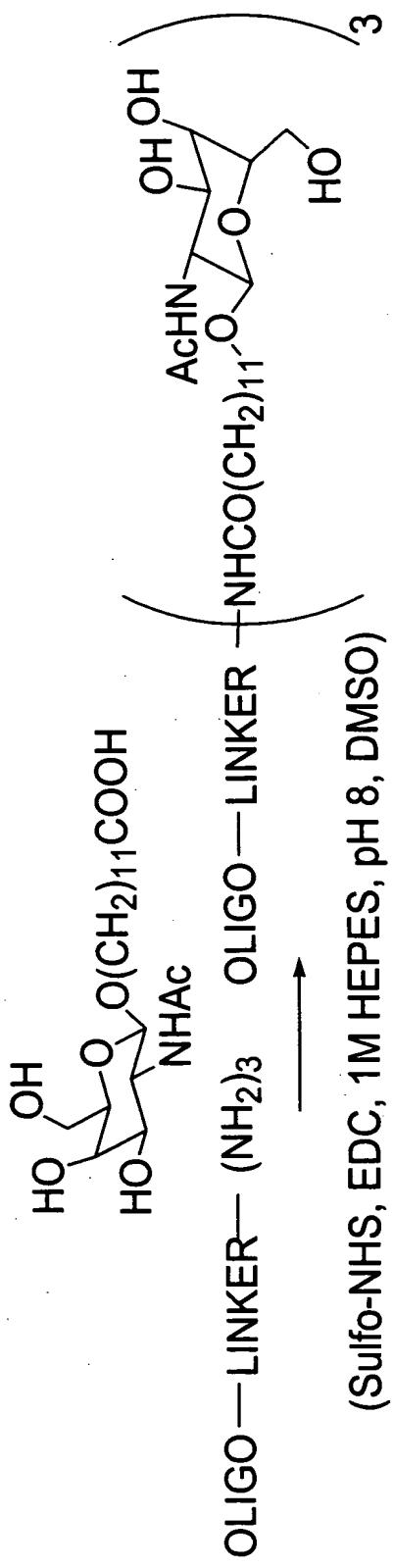
**Figure 21: 40-KDa PEG-Angiozyme vs Angiozyme**



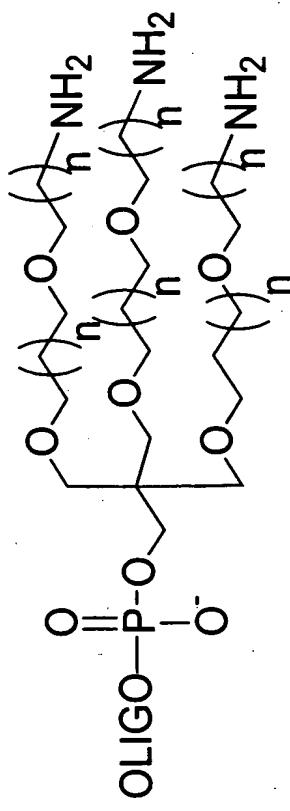
*Figure 22: Phospholipid-Angiozyme vs Angiozyme*



**Figure 23: Oligonucleotide-NAcGalactosamine post-synthetic coupling**

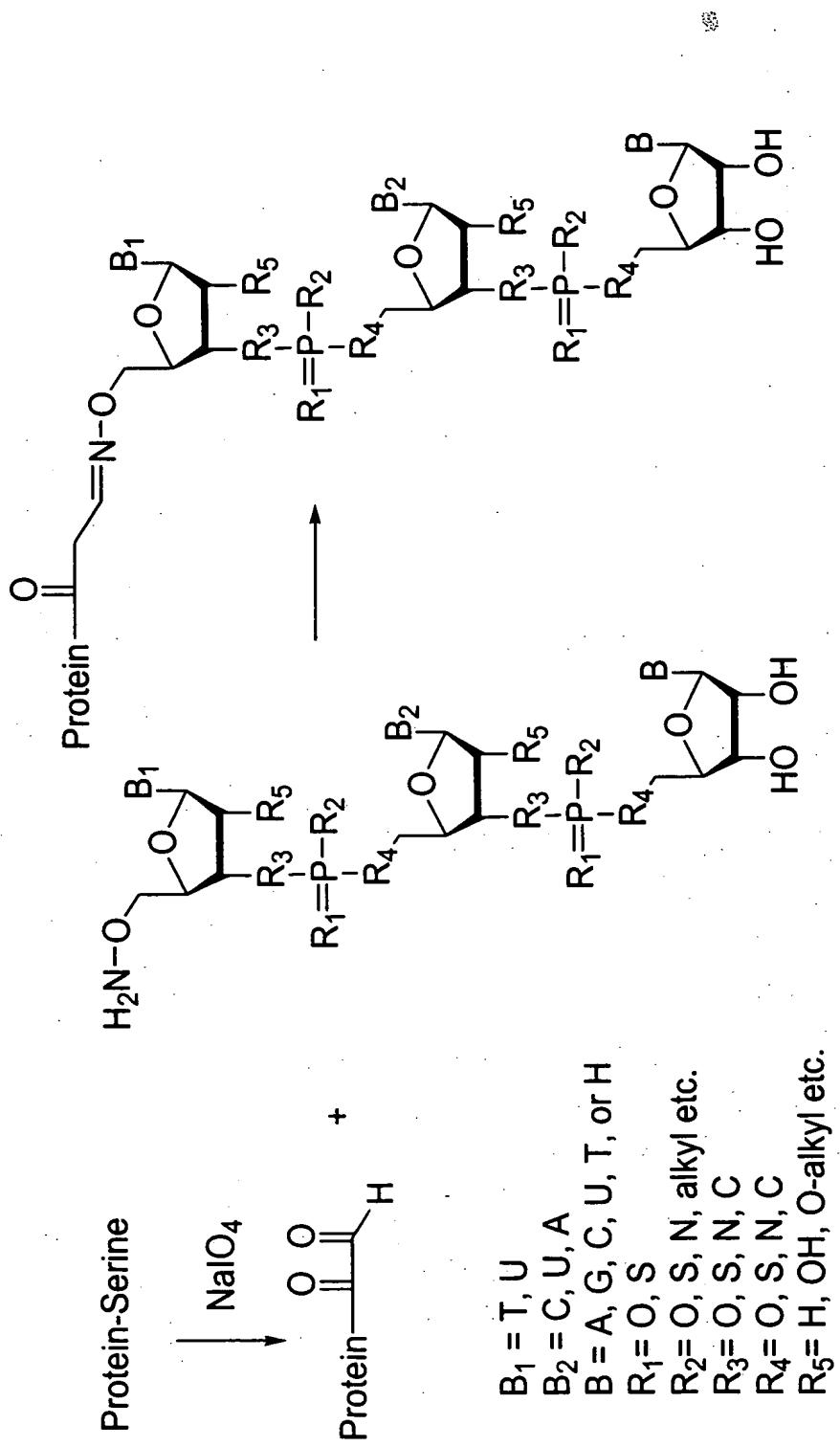


FOR EXAMPLE: OLIGO-LINKER =

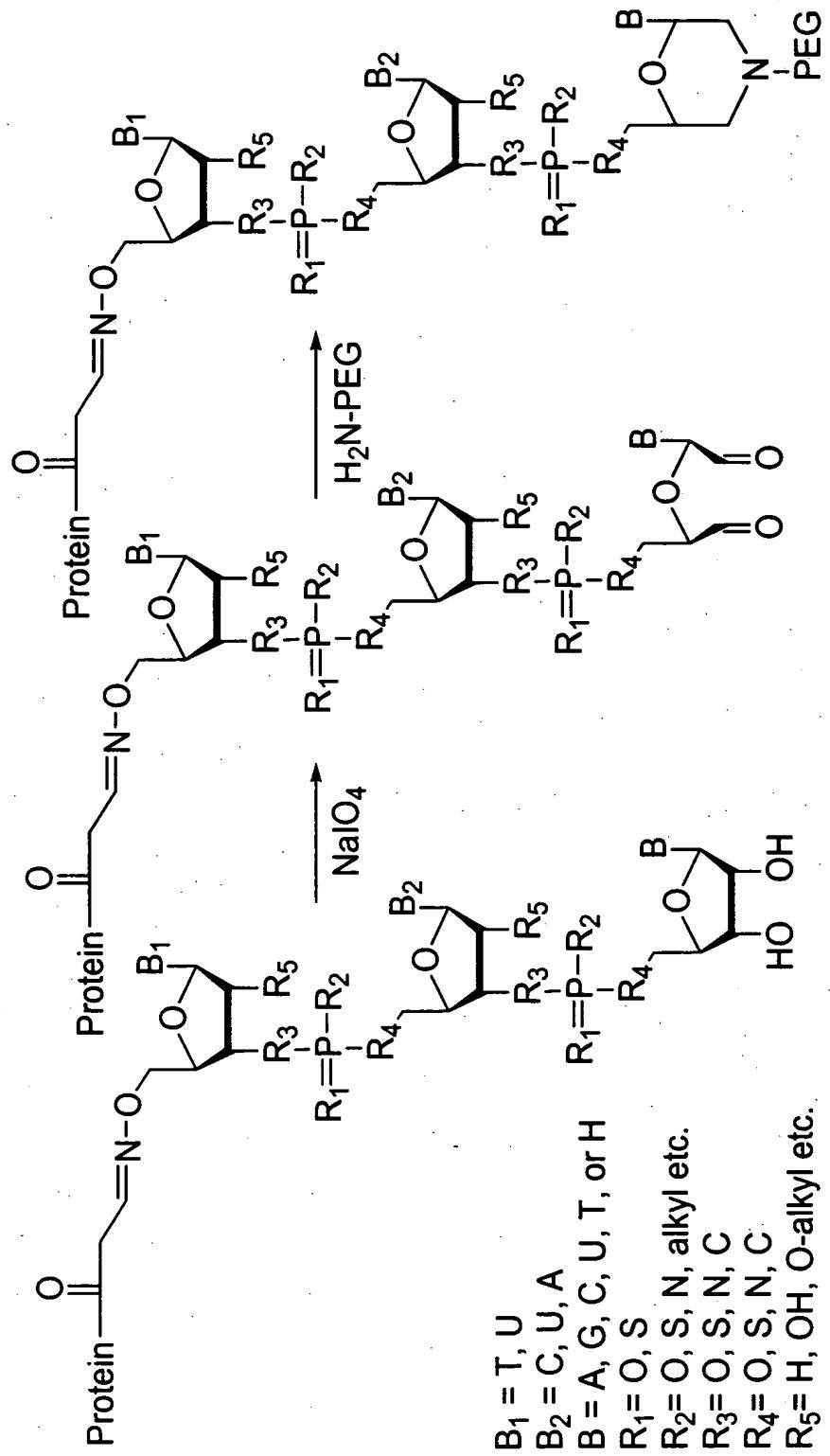


Where  $n$  is an integer from 1 to 20

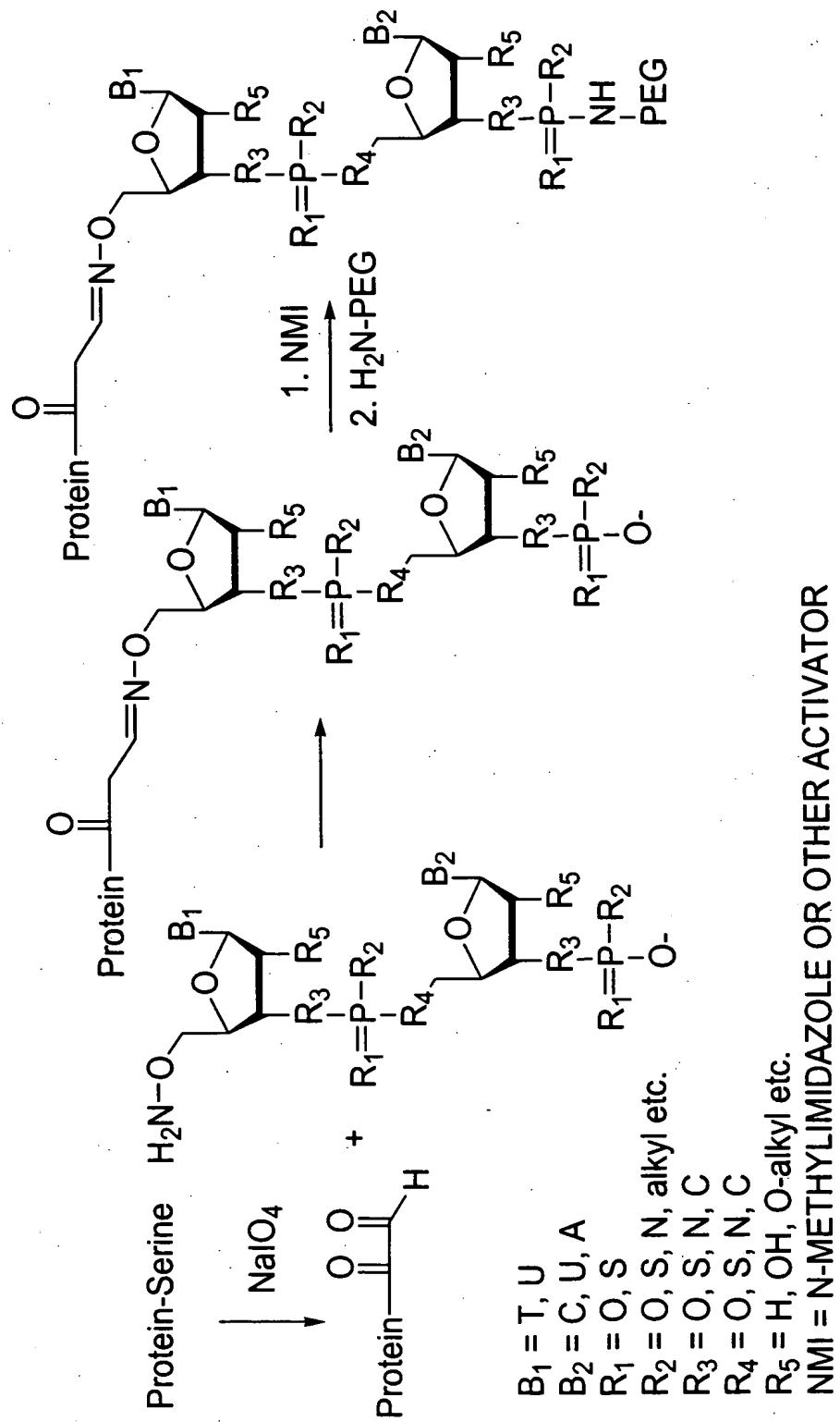
**Figure 24a:** Protein with cleavable linker



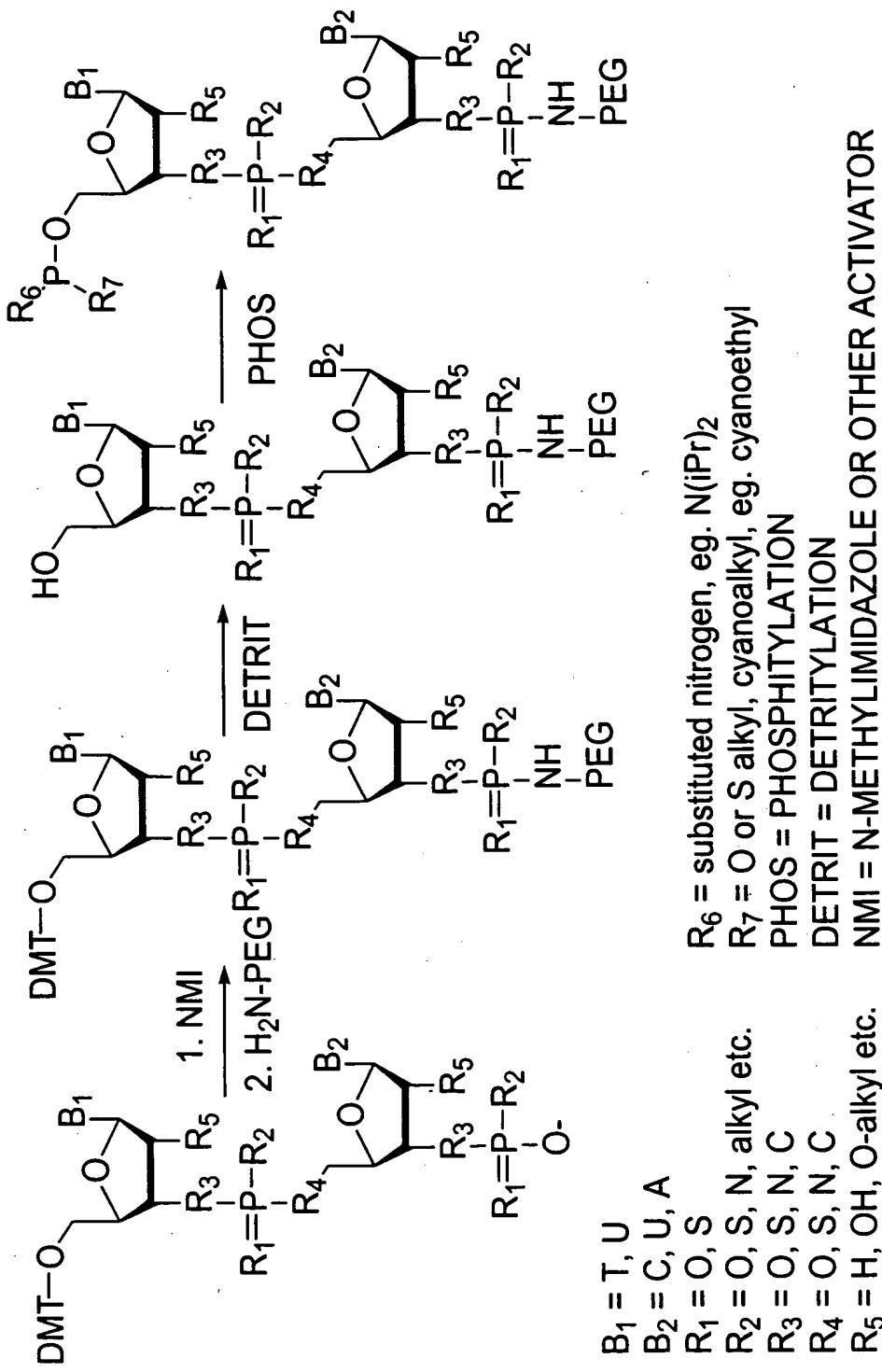
**Figure 24b: Protein cleavable linker PEG Conjugate**



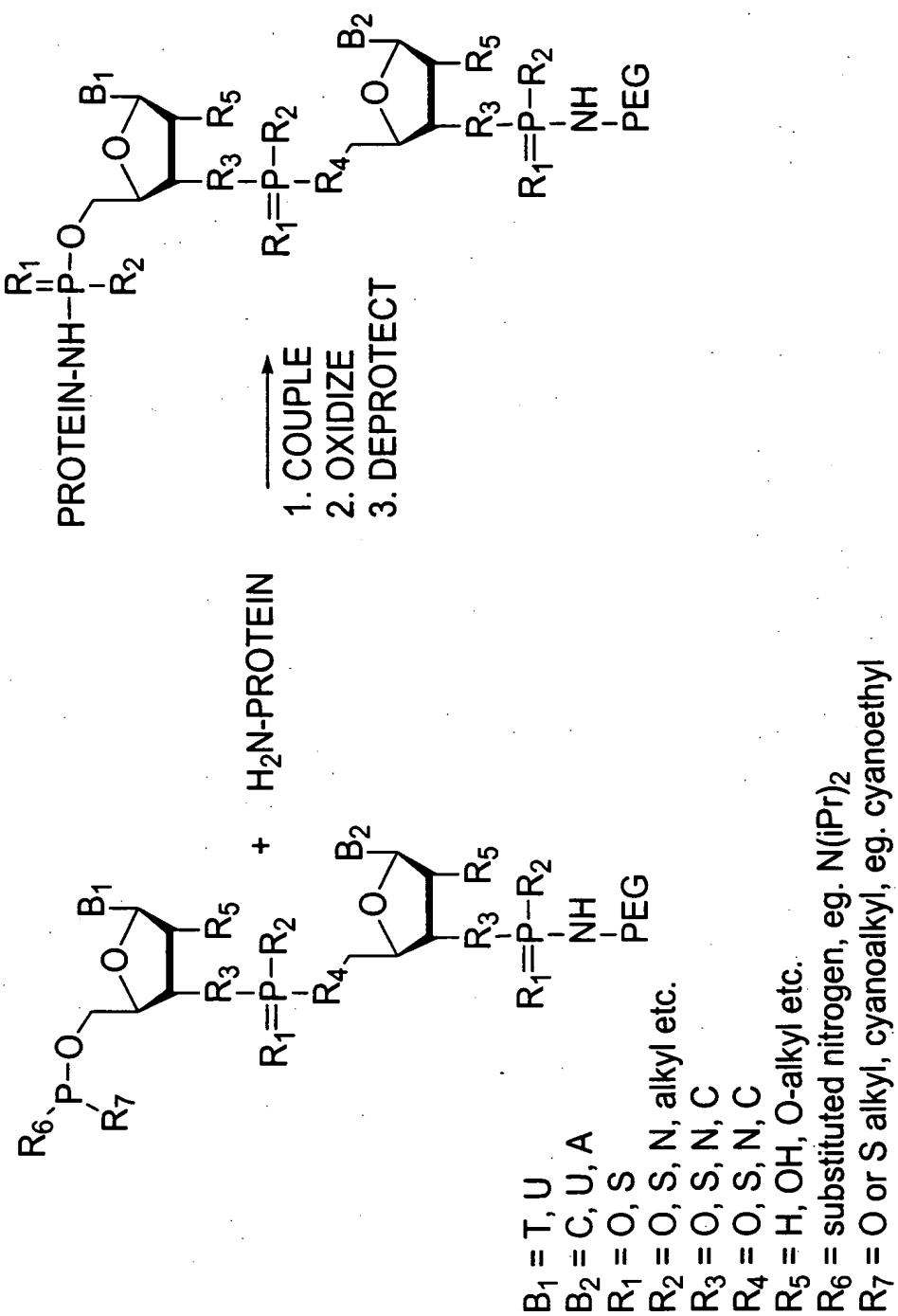
**Figure 25: Protein PEG conjugate with cleavable linker**



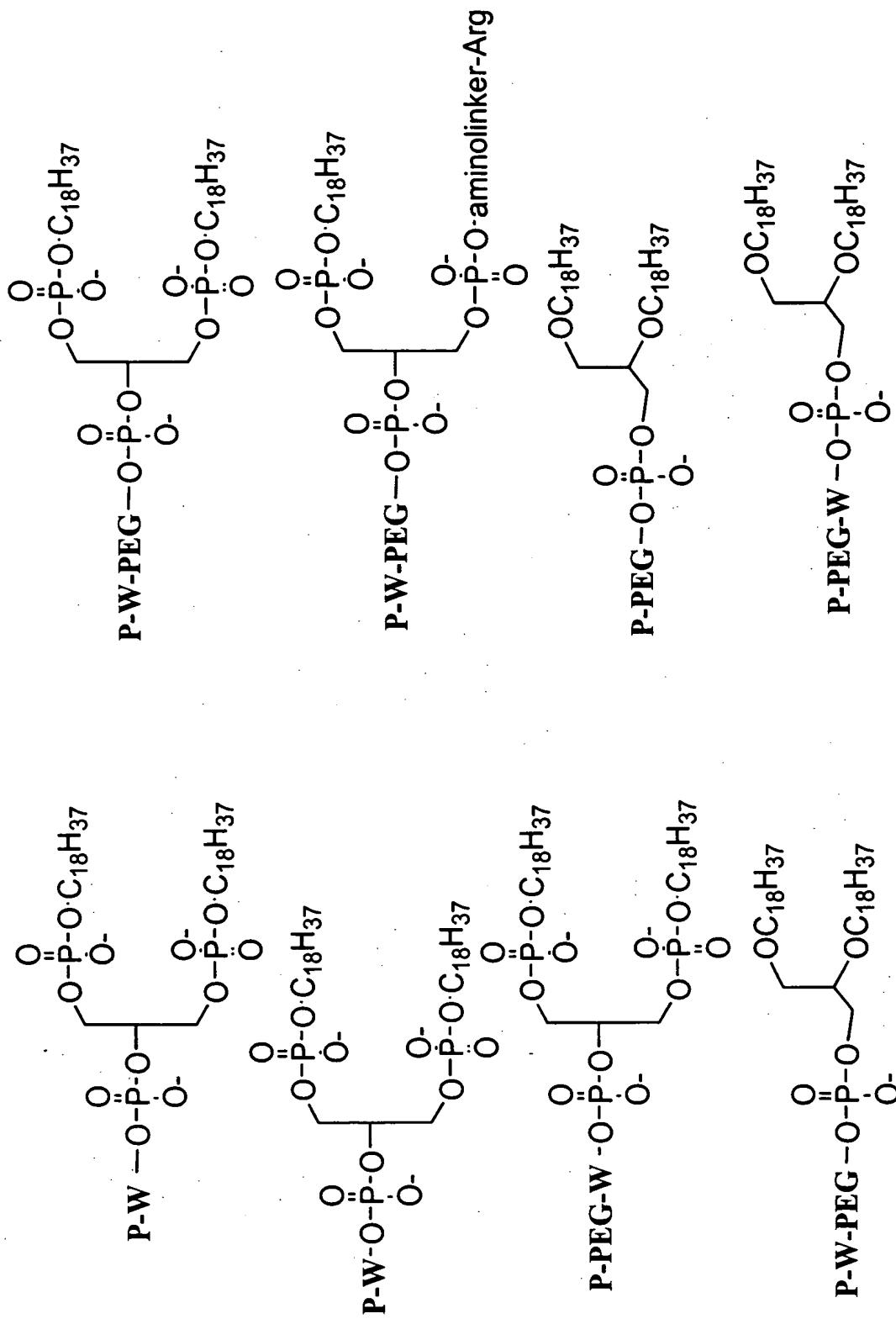
**Figure 26a: PEG with cleavable linker**



**Figure 26b: Protein PEG conjugate with cleavable linker**

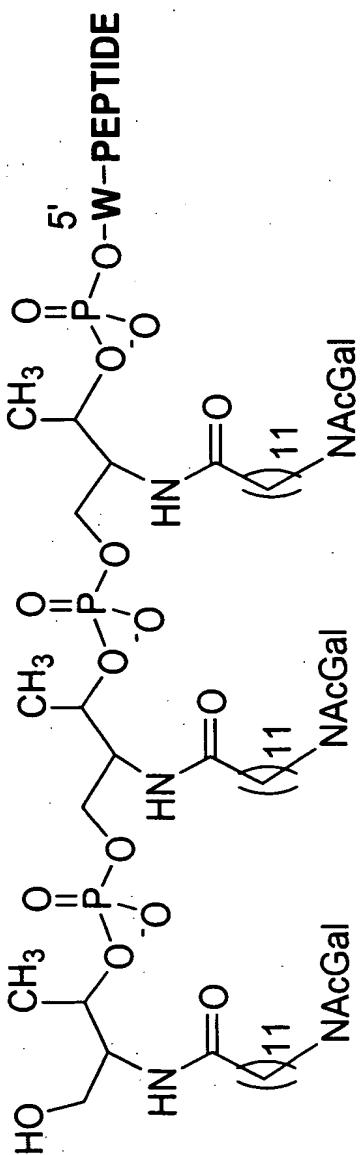


**Figure 27: Peptide or Protein/Phospholipid Conjugates**



PEG=polyethylene glycol  
 W=cleavable linker (e.g. A-dT, C-dT)  
 P=Peptide/Protein

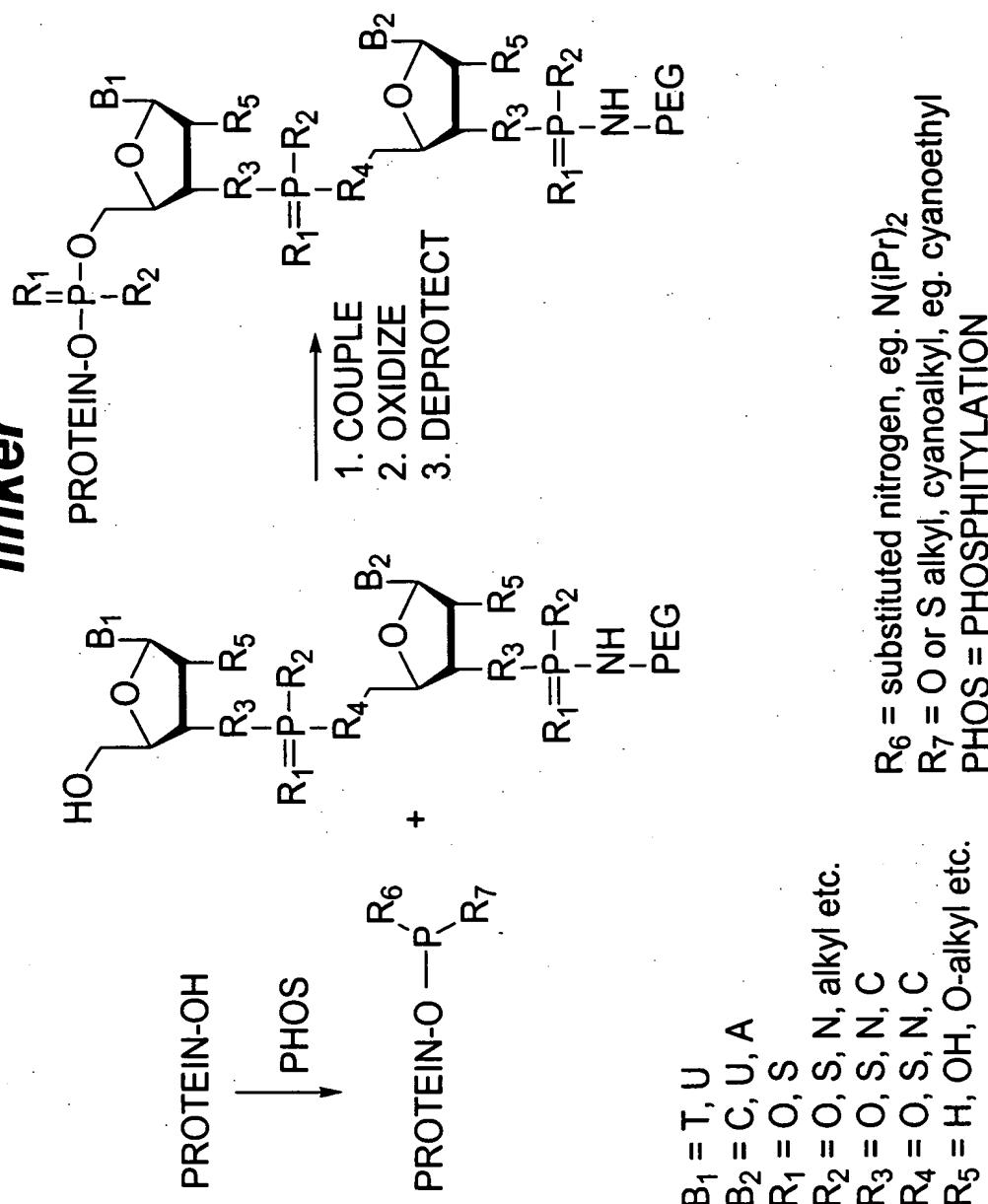
**Figure 28: Conjugation of targeting ligands to a peptide or protein**



*N*-acetyl-D-galactosamine conjugate

**W = cleavable linker (eg. A-dT, C-dT dimer)**

**Figure 29: Protein/PEG conjugate with cleavable linker**



*Figure 30: siNA Cholesterol Conjugate*

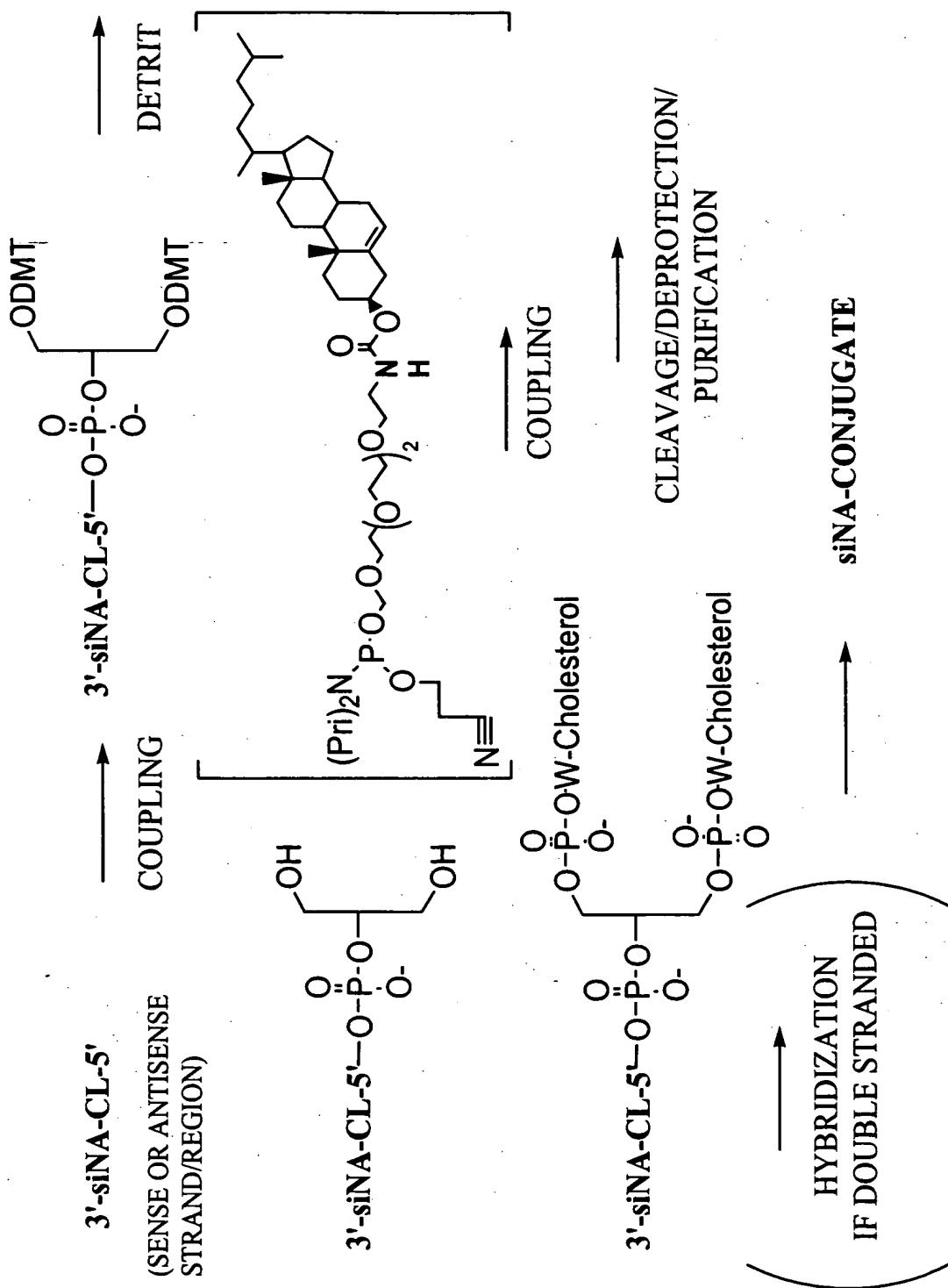
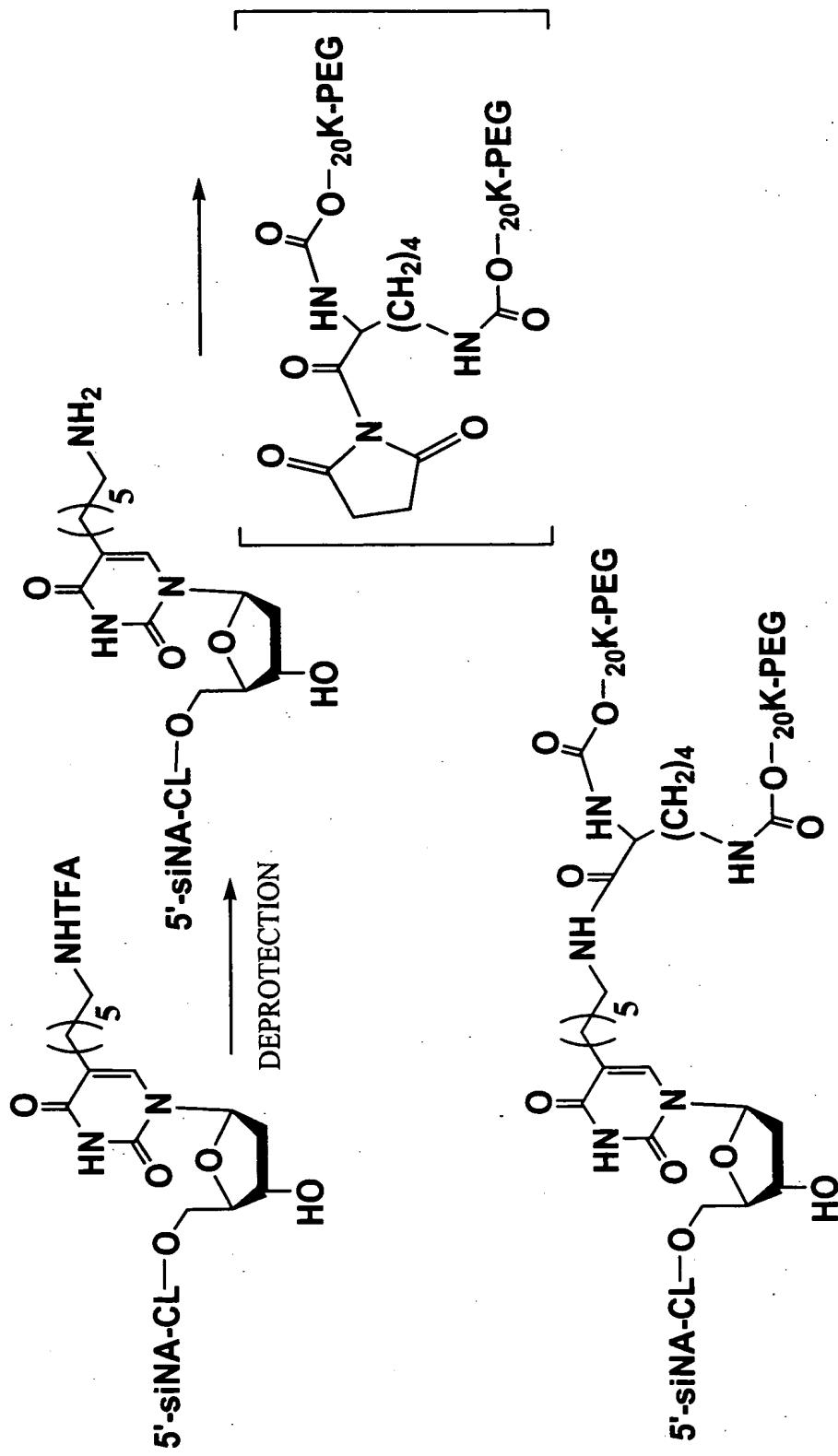
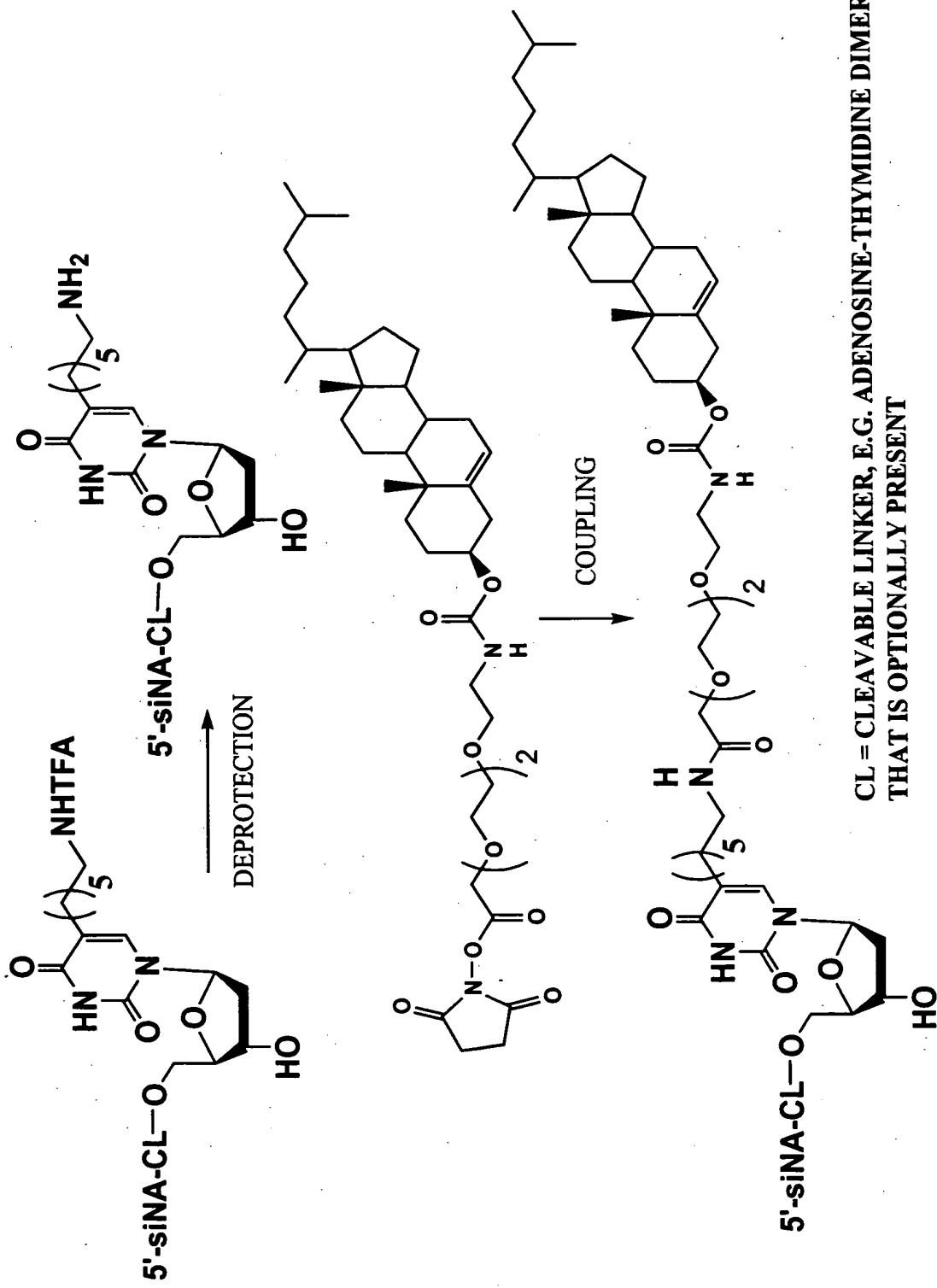


Figure 31: siNA 3'-PEG Conjugate

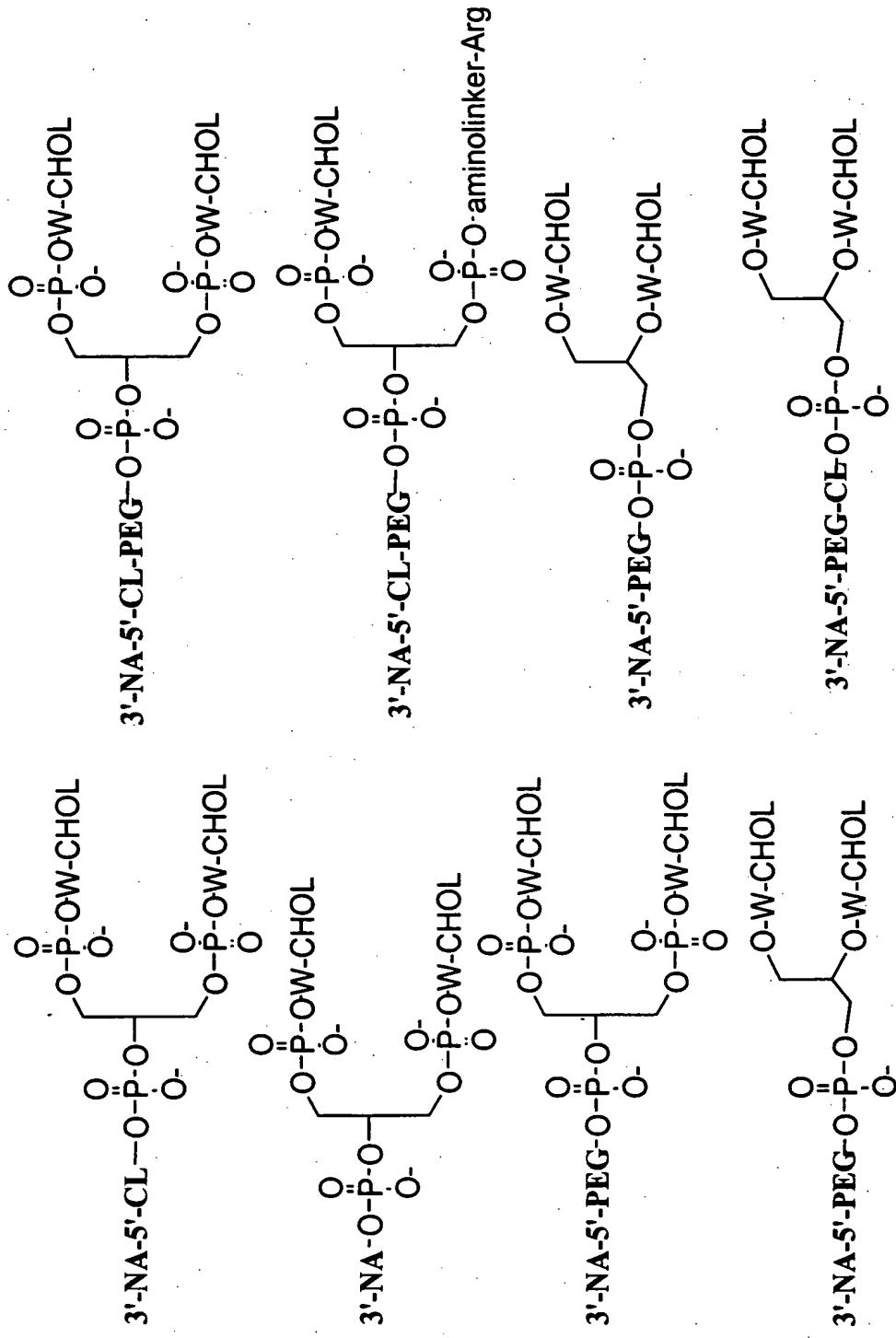


CL = CLEAVABLE LINKER, E.G. ADENOSINE-THYMIDINE DIMER  
THAT IS OPTIONALLY PRESENT

**Figure 32:** siNA 3'-Cholesterol Conjugate



**Figure 33: Nucleic Acid Cholesterol Conjugates**



PEG=polyethylene glycol

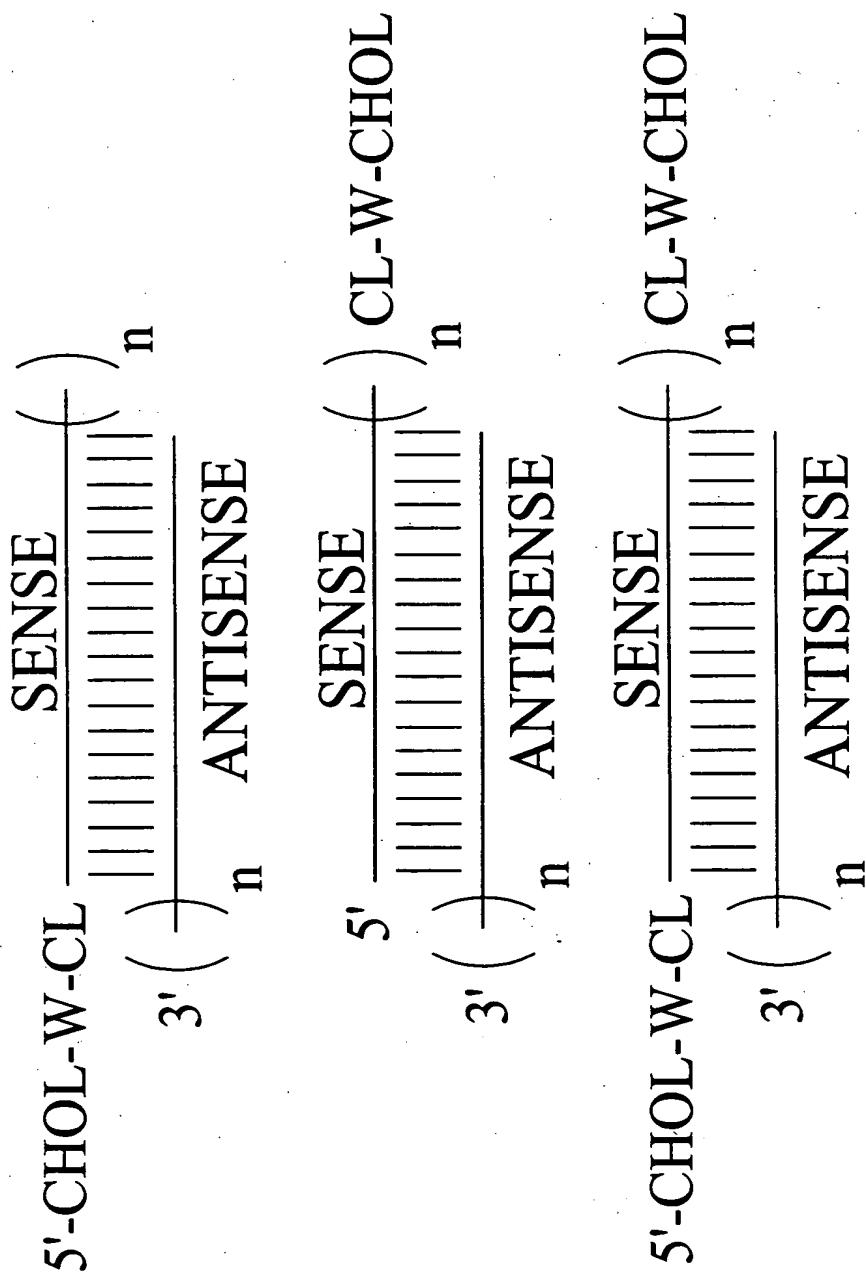
CL=cleavable linker (e.g. A-dT, C-dT)

NA=Nucleic Acid Molecule such as siNA, antisense, or enzymatic nucleic acid

CHOL=cholesterol or an analog or metabolite thereof

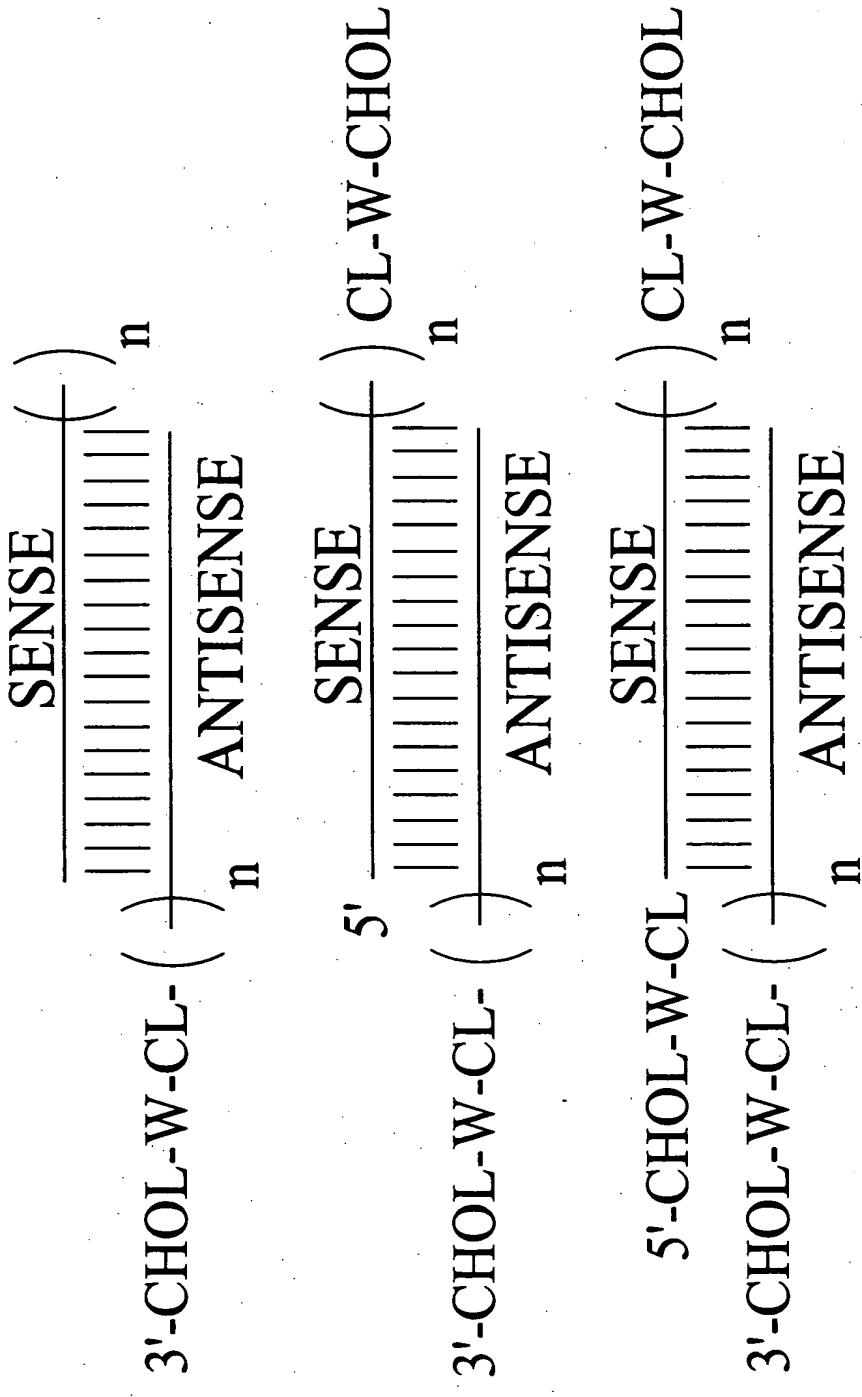
W=linker molecule (see for example Formulae 109 or 112)

*Figure 34: siNA Cholesterol Conjugates*



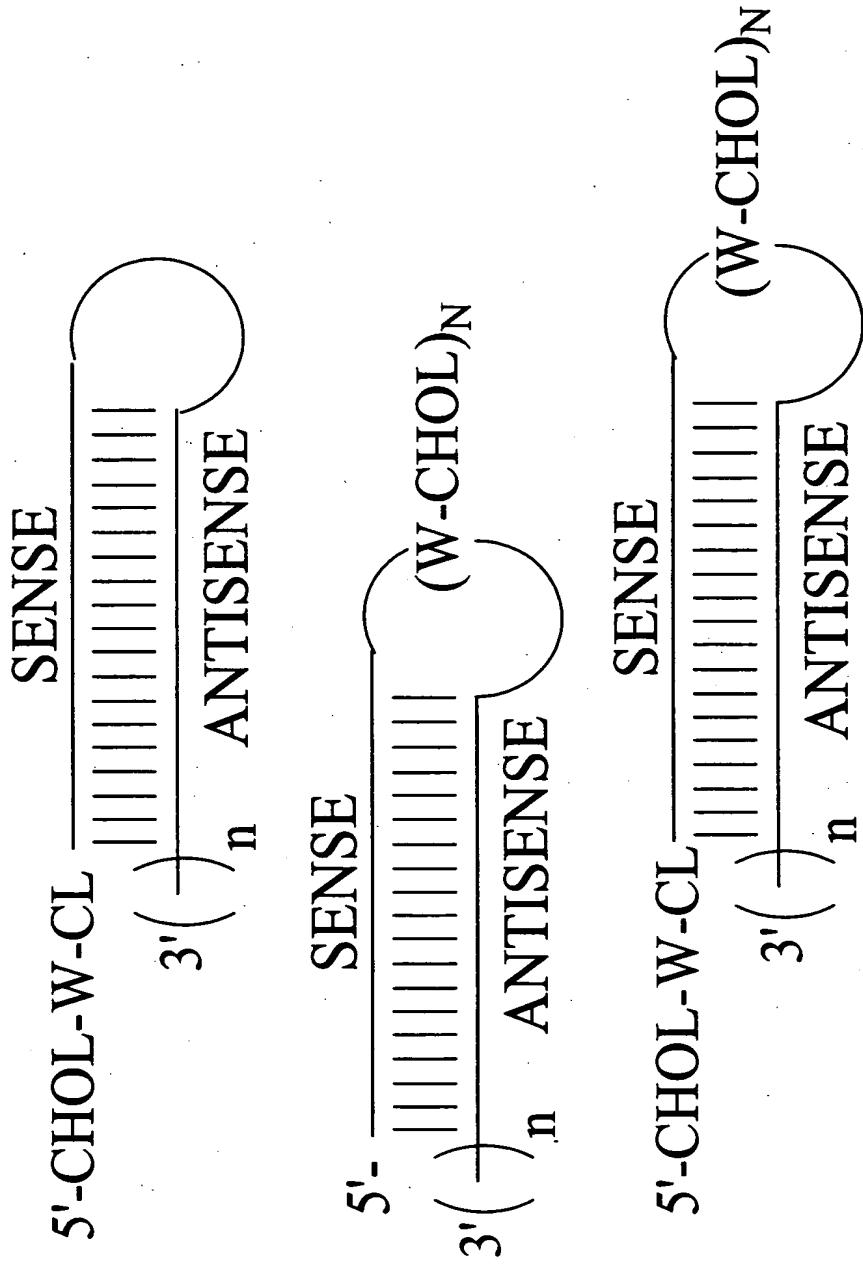
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 CHOL=cholesterol or an analog or metabolite thereof  
 WW=linker molecule (see for example Formulae 107, 108, 109 or 115  
 n = integer, e.g. 1, 2, or 3

*Figure 35: siNA Cholesterol Conjugates*



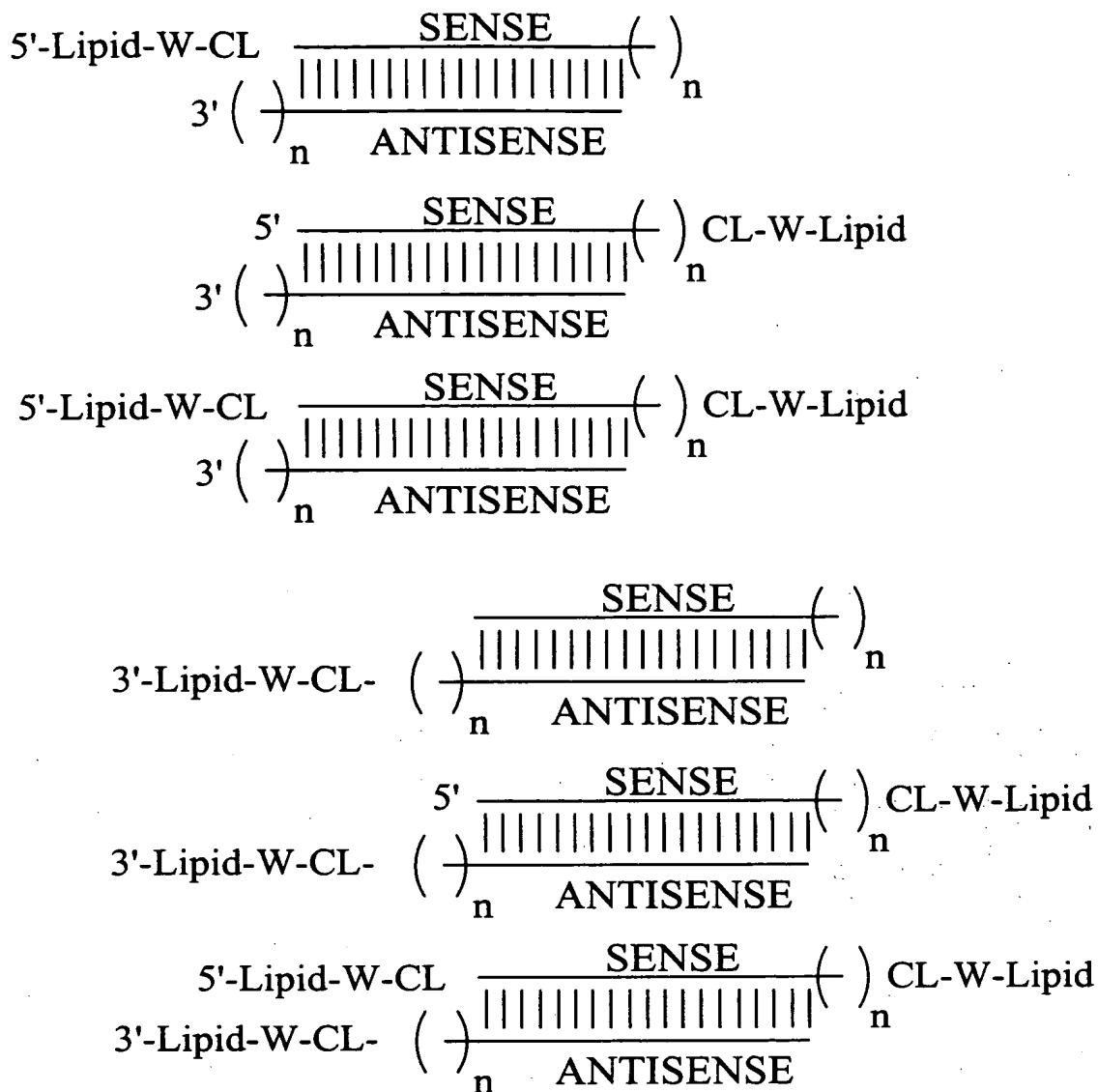
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
CHOL=cholesterol or an analog or metabolite thereof  
W=linker molecule (see for example Formulae 107, 108, 109 or 115)  
n = integer, e.g. 1, 2, or 3

**Figure 36: siNA Cholesterol Conjugates**



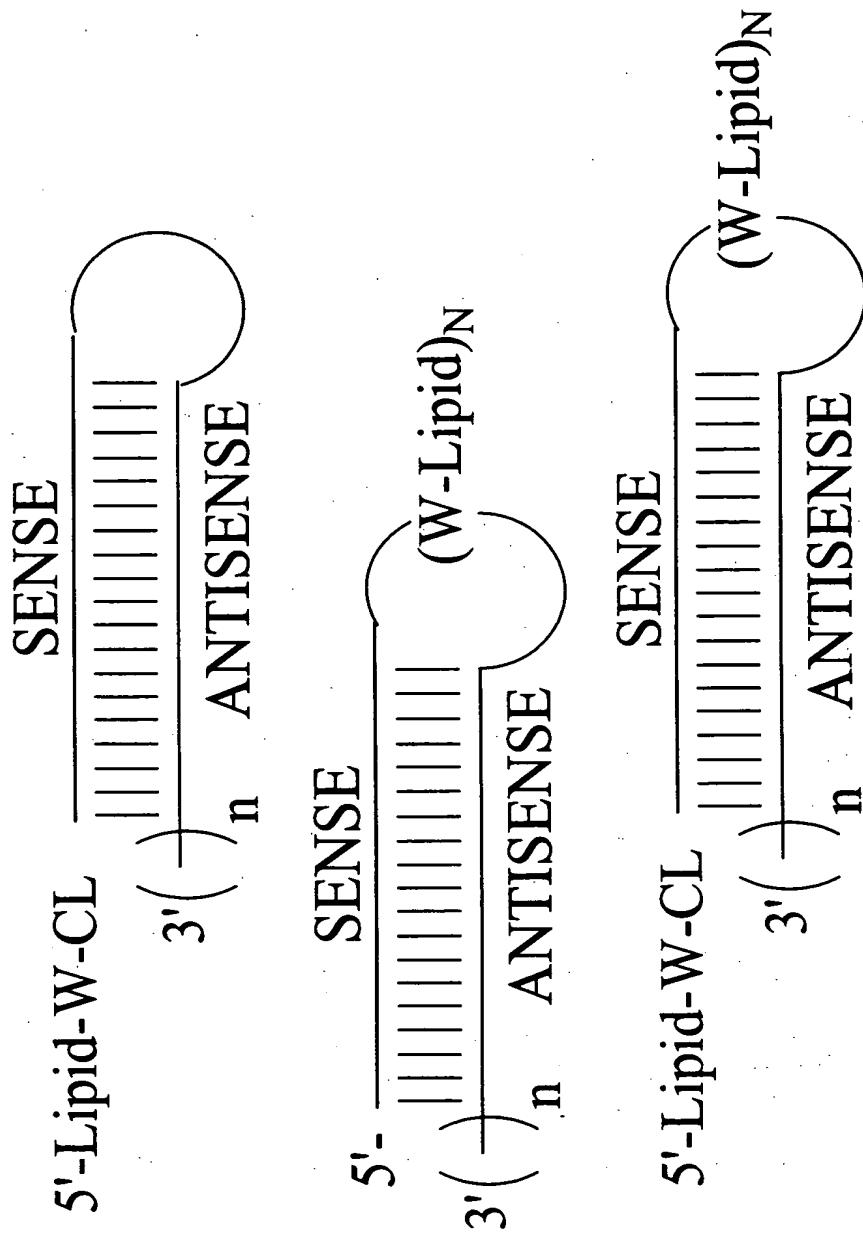
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
CHOL=cholesterol or an analog or metabolite thereof  
W=linker molecule (see for example Formulae 107, 108, 109 or 112)  
n = integer, e.g. 1, 2, 3, or 3  
N=integer, e.g. 1, 2, 3, or 4

### **Figure 37: siNA Lipid Conjugates**



**CL**=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
**Lipid**=Straight chain or branched alkyl or fatty acid, e.g. C<sub>18</sub>H<sub>37</sub>  
**W**=linker molecule (see for example Formulae 48, 49, 64, or 65)  
**n**=integer, e.g. 1, 2, or 3

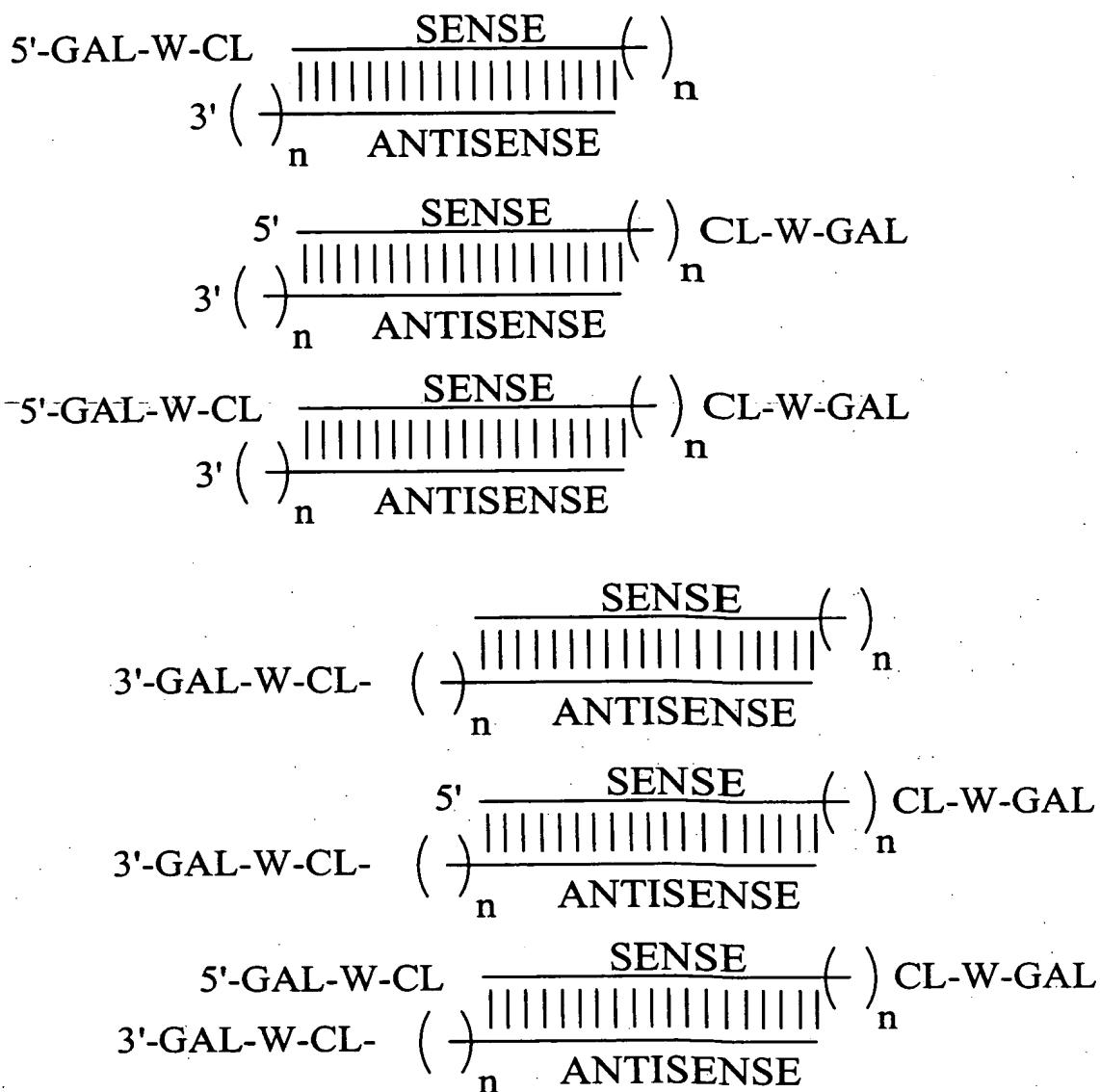
**Figure 38: siNA Lipid Conjugates**



CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
Lipid=Straight chain or branched alkyl or fatty acid, e.g. C<sub>18</sub>H<sub>37</sub>  
W=linker molecule (see for example Formulae 48, 49, 64, or 65)

n = integer, e.g. 1, 2, 3, or 4  
N=integer, e.g. 1, 2, 3, or 4

**Figure 39: siNA Galactosamine Conjugates**



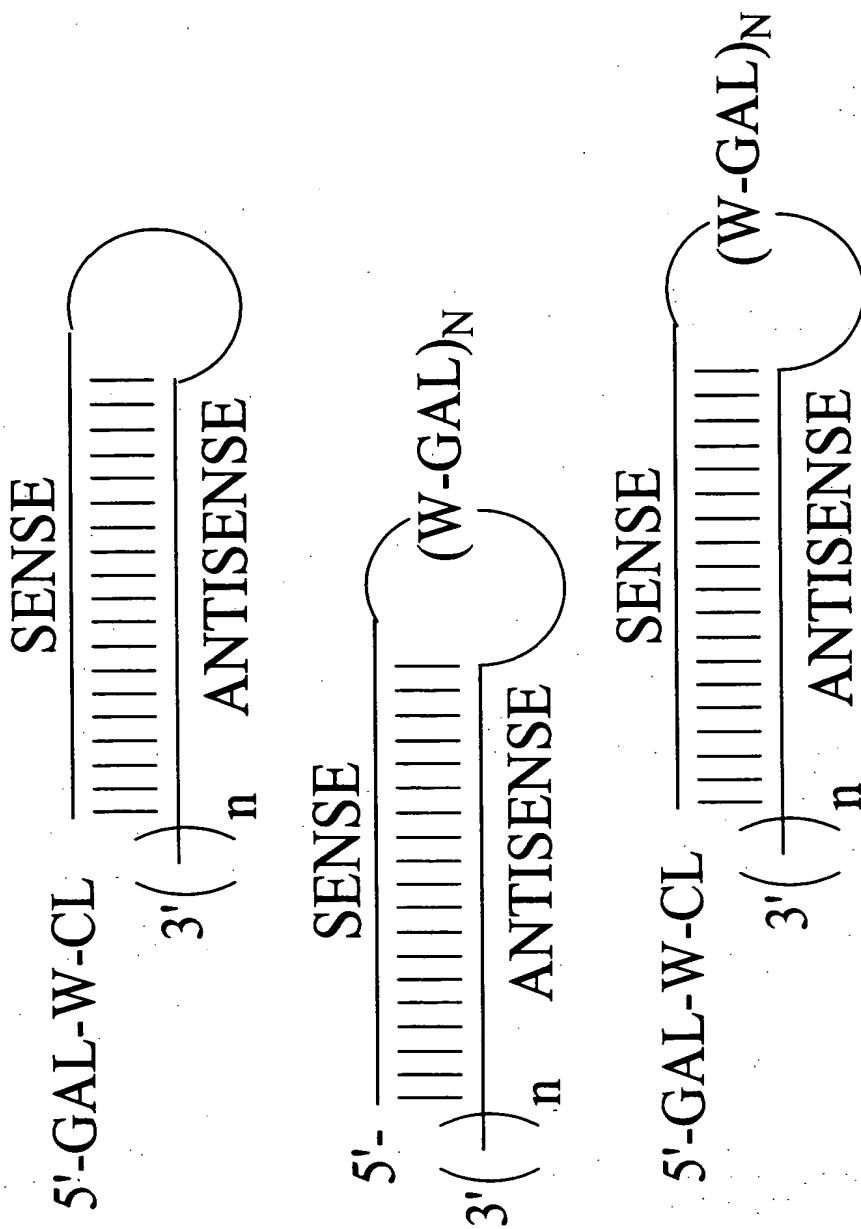
**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**

**GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106**

**W= linker molecule (see for example Formulae 102 or 103)**

**n = integer, e.g. 1, 2, or 3**

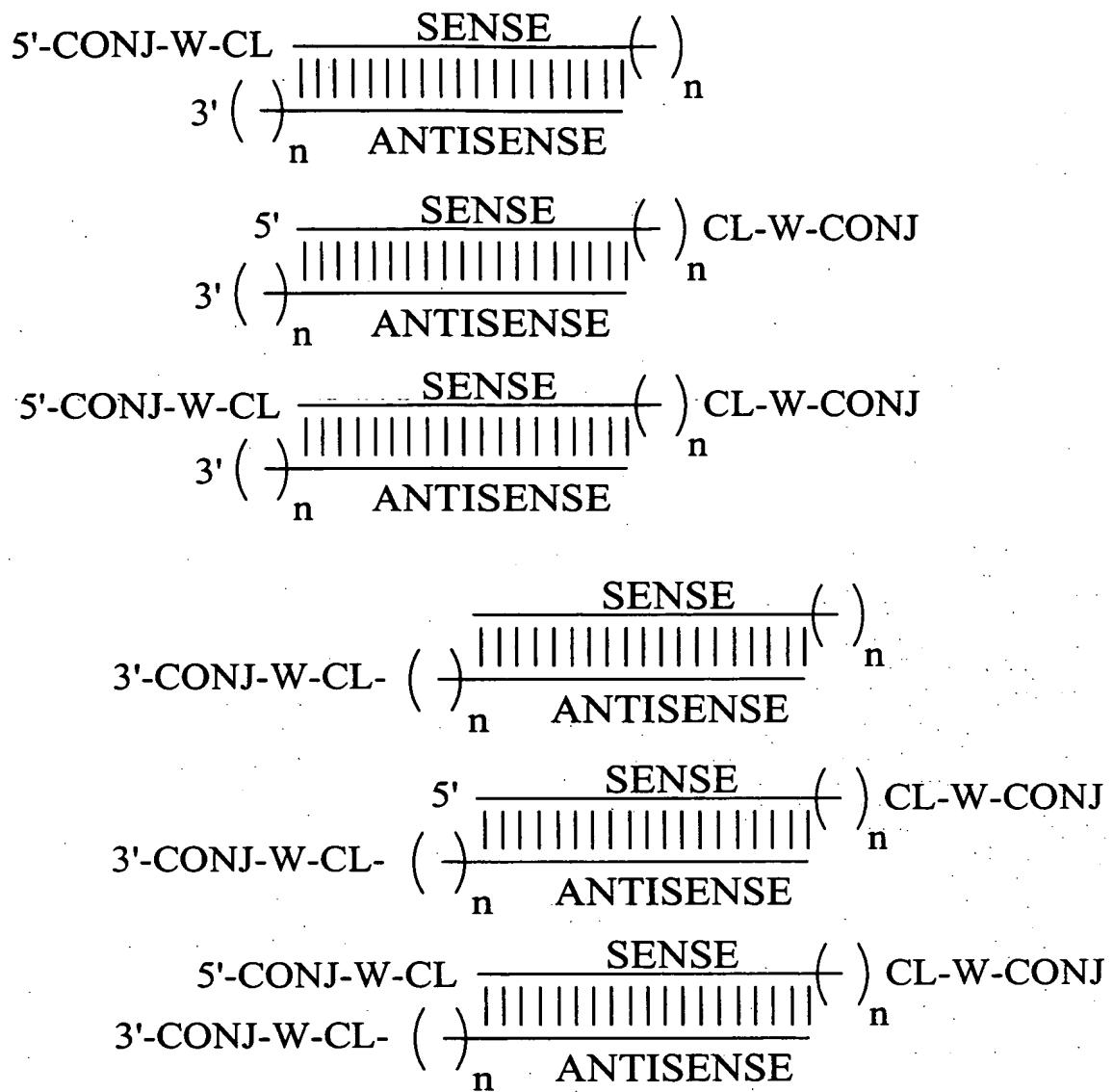
**Figure 40: siNA Galactosamine Conjugates**



CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106  
W=linker molecule (see for example Formulae 102 or 103)

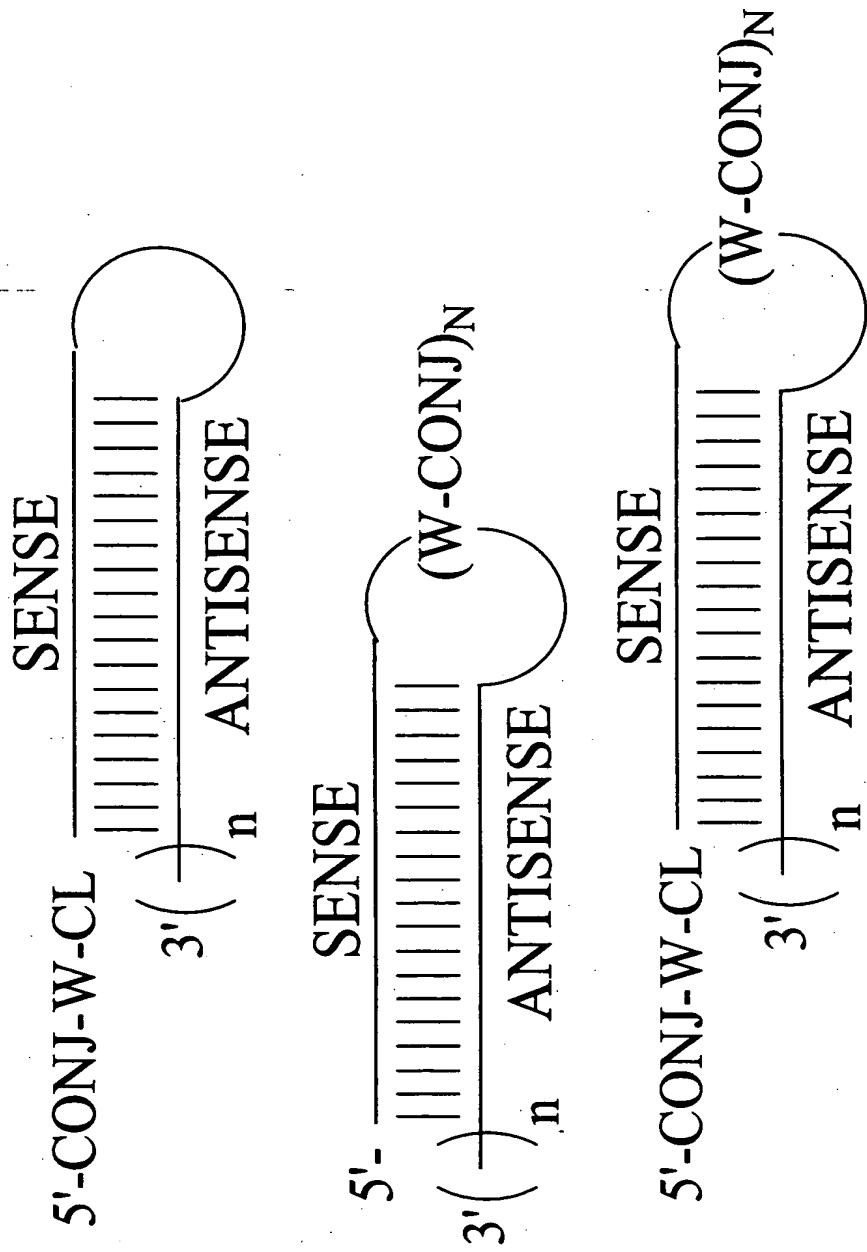
n = integer, e.g. 1, 2, or 3  
N=integer, e.g. 1, 2, 3, or 4

**Figure 41: Generalized siNA Conjugate Design**



**CONJ**=any biologically active molecule or conjugate as described herein  
**CL**=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
**W**=linker molecule  
**n**=integer, e.g. 1, 2, or 3

*Figure 42: Generalized siNA Conjugate design*



CONJ=any biologically active molecule or conjugate as described herein

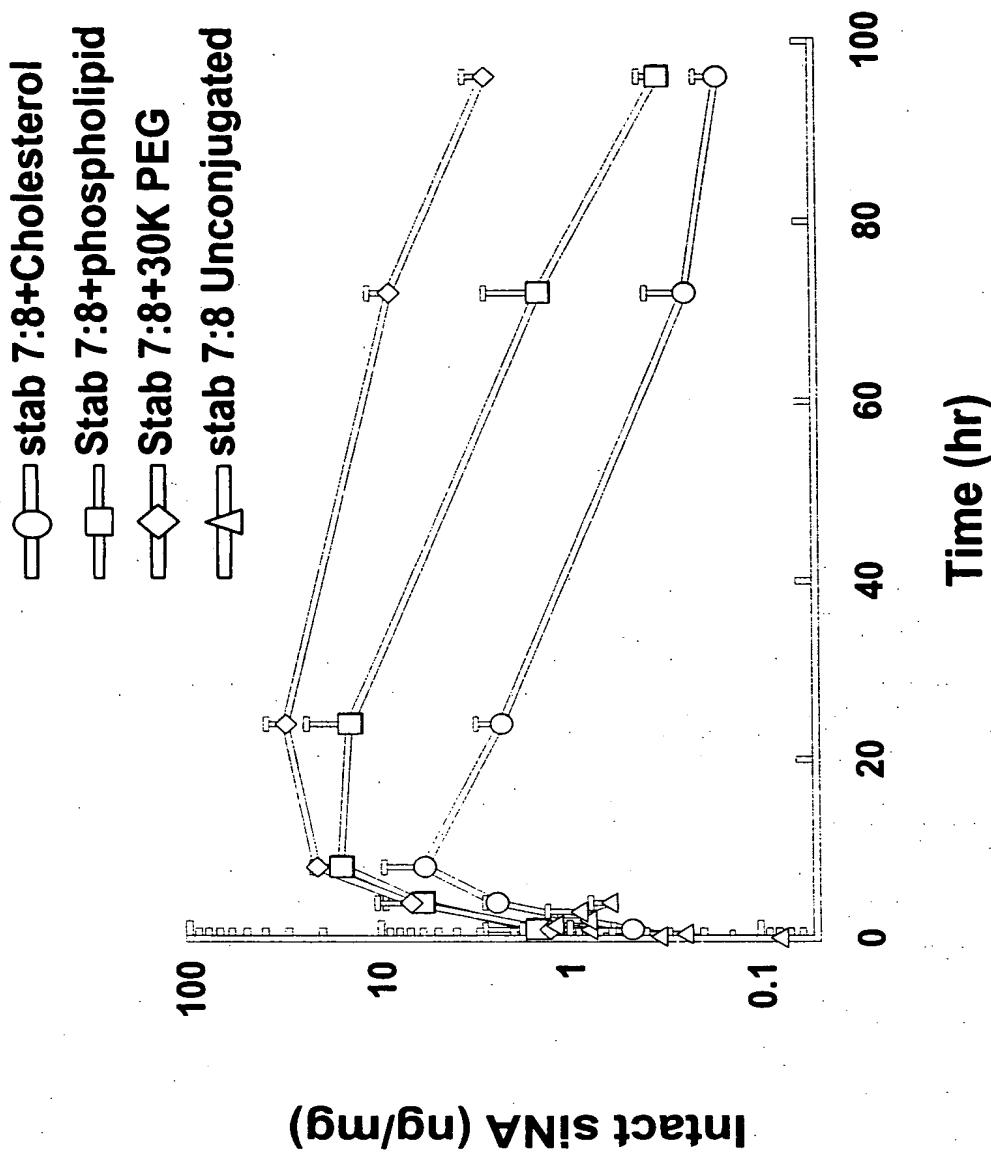
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

W=linker molecule

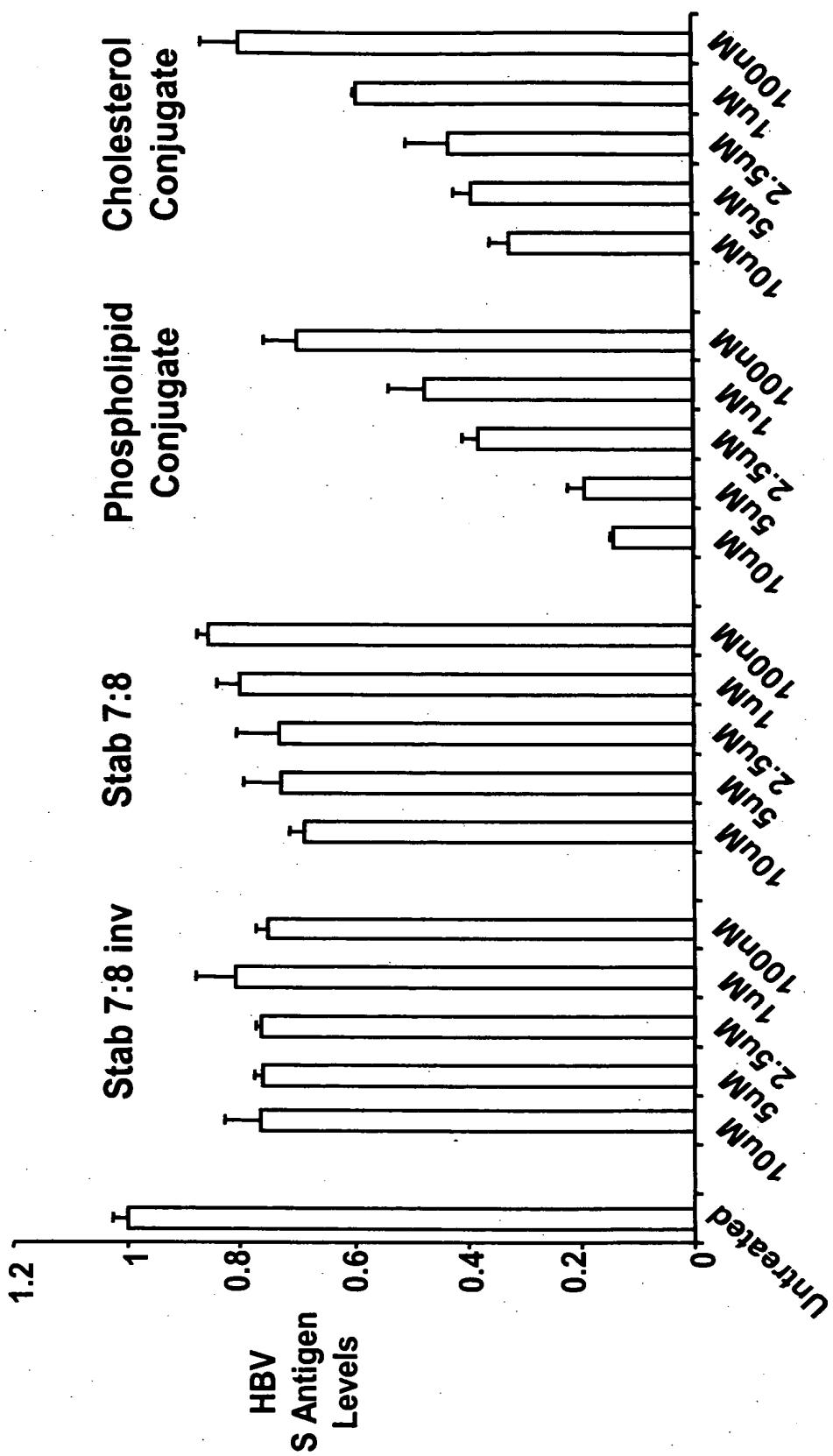
n = integer, e.g. 1, 2, or 3

N=integer, e.g. 1, 2, 3, or 4

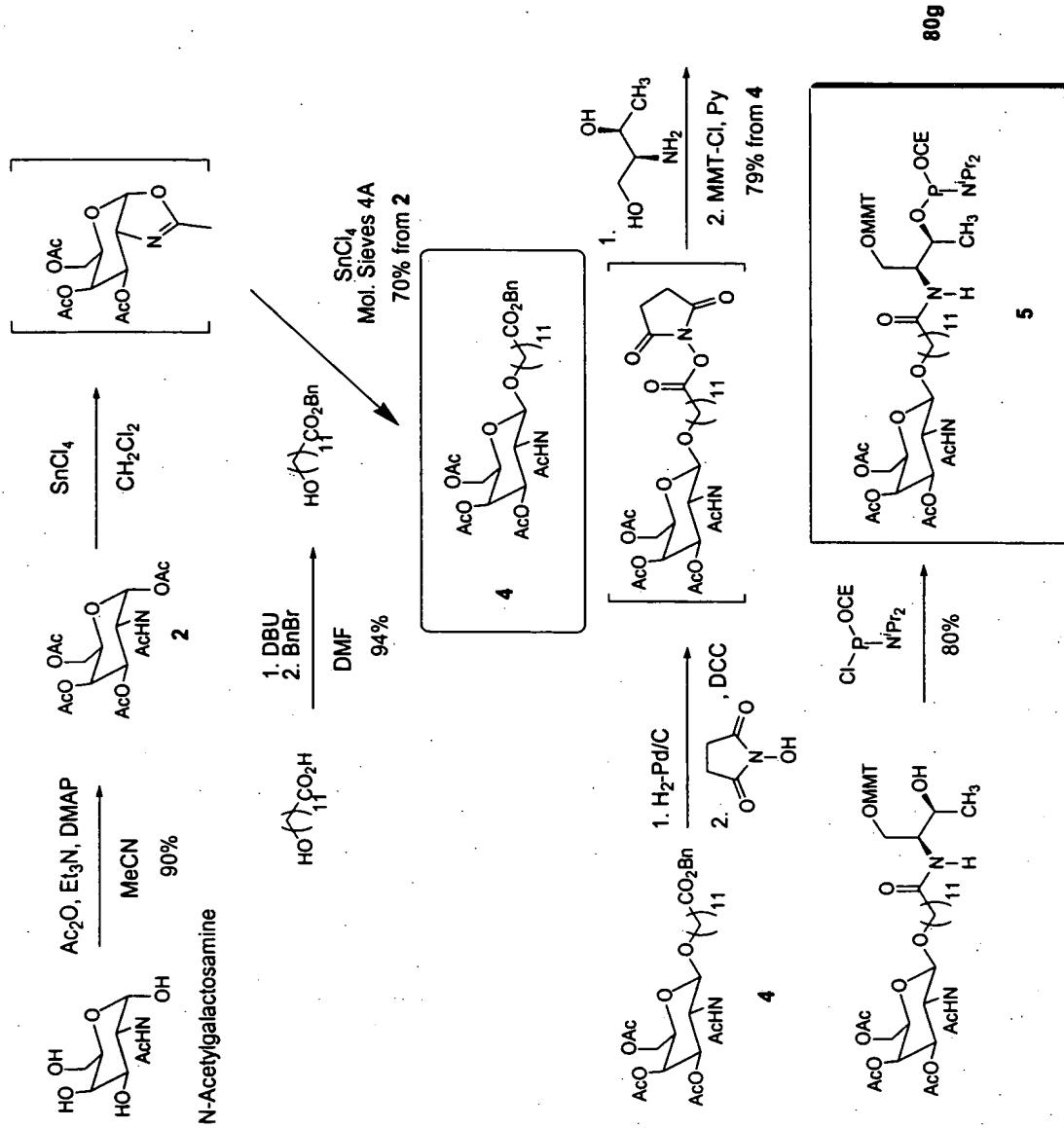
**Figure 43: Distribution of Intact siNA in Liver After SC Administration of Conjugated or Unconjugated Chemistries**



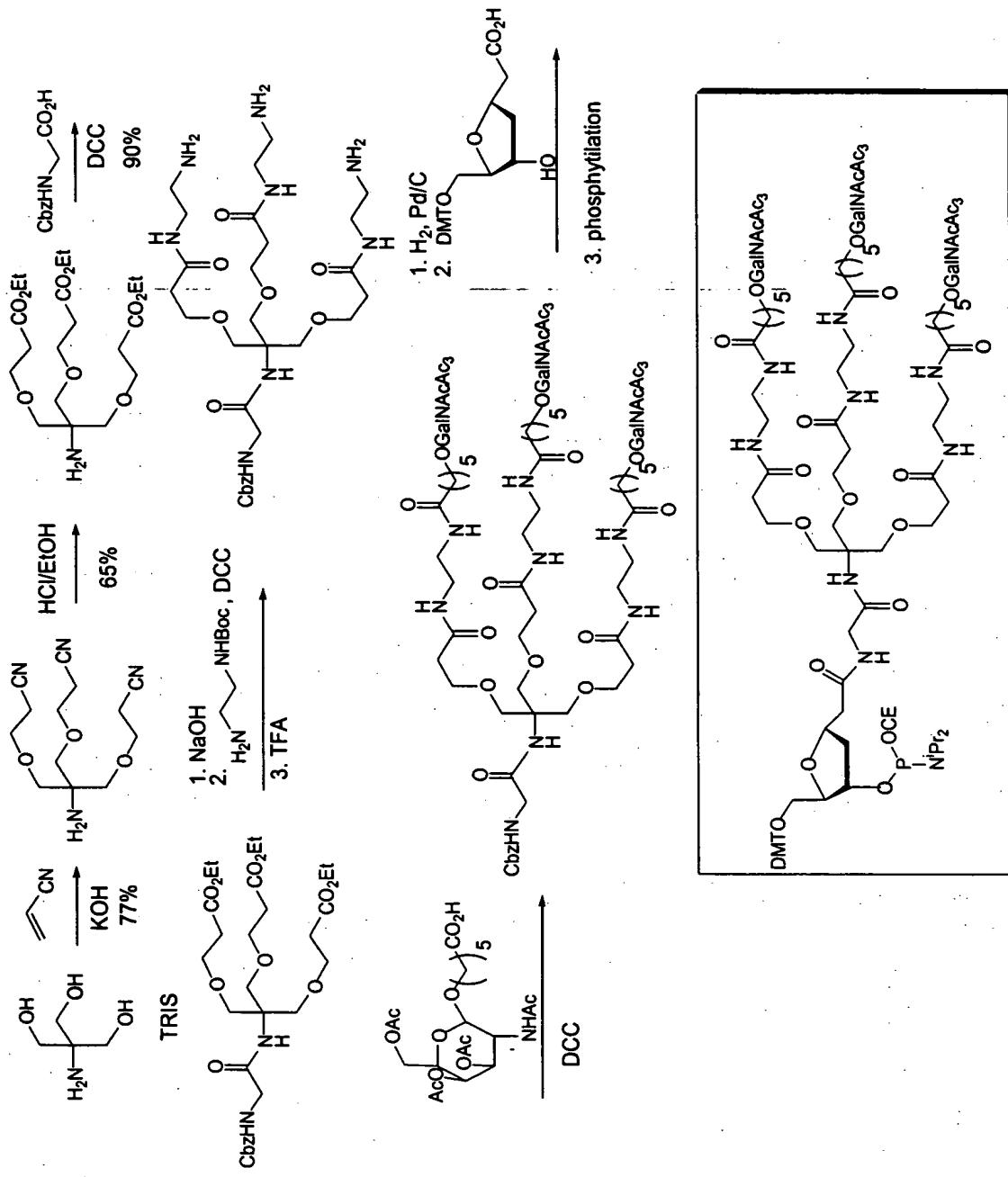
**Figure 44: Lipid Free Delivery of HBV siNA Conjugates in Cell Culture**



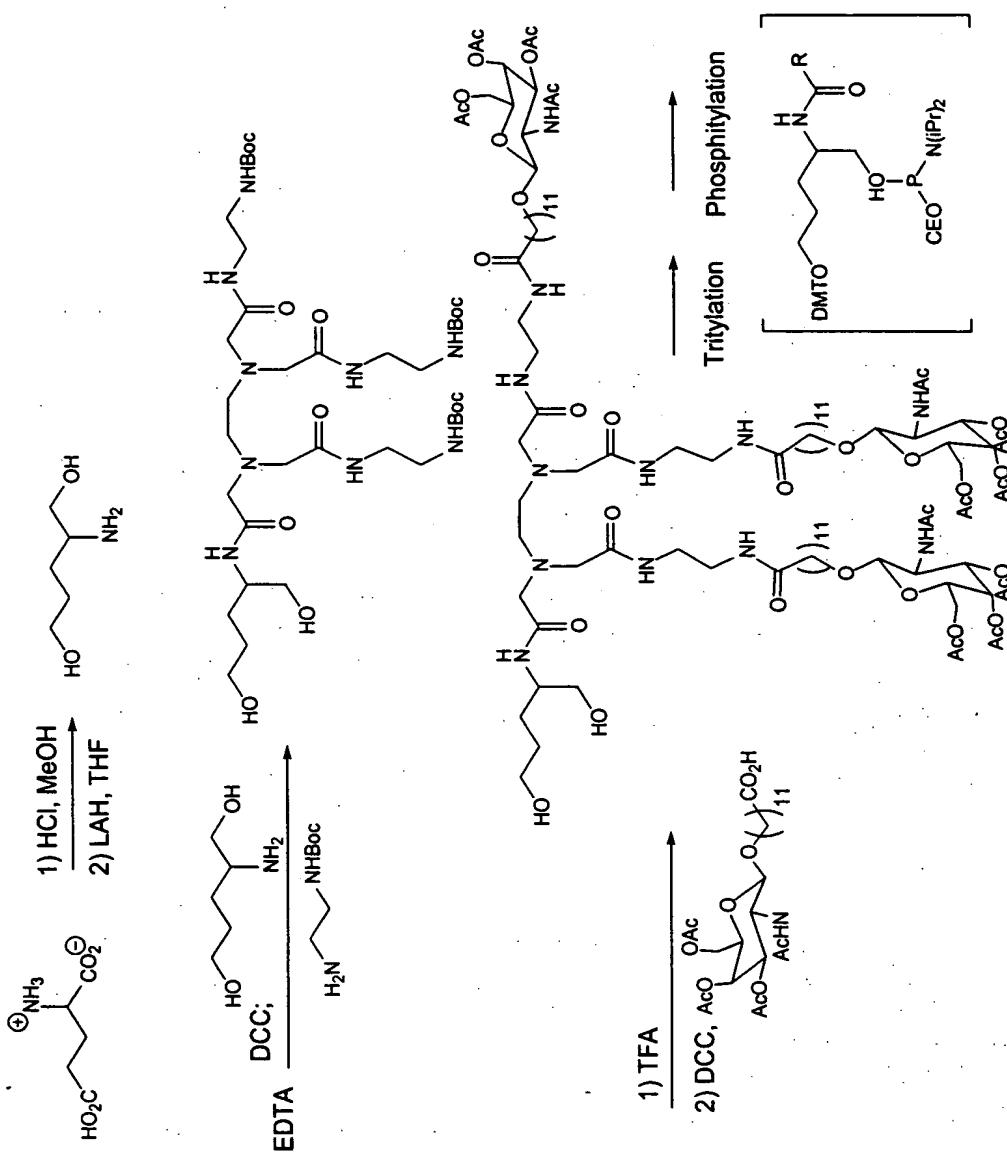
**Figure 45: Scale-up of "mono" Galactosamine phosphoramidite**



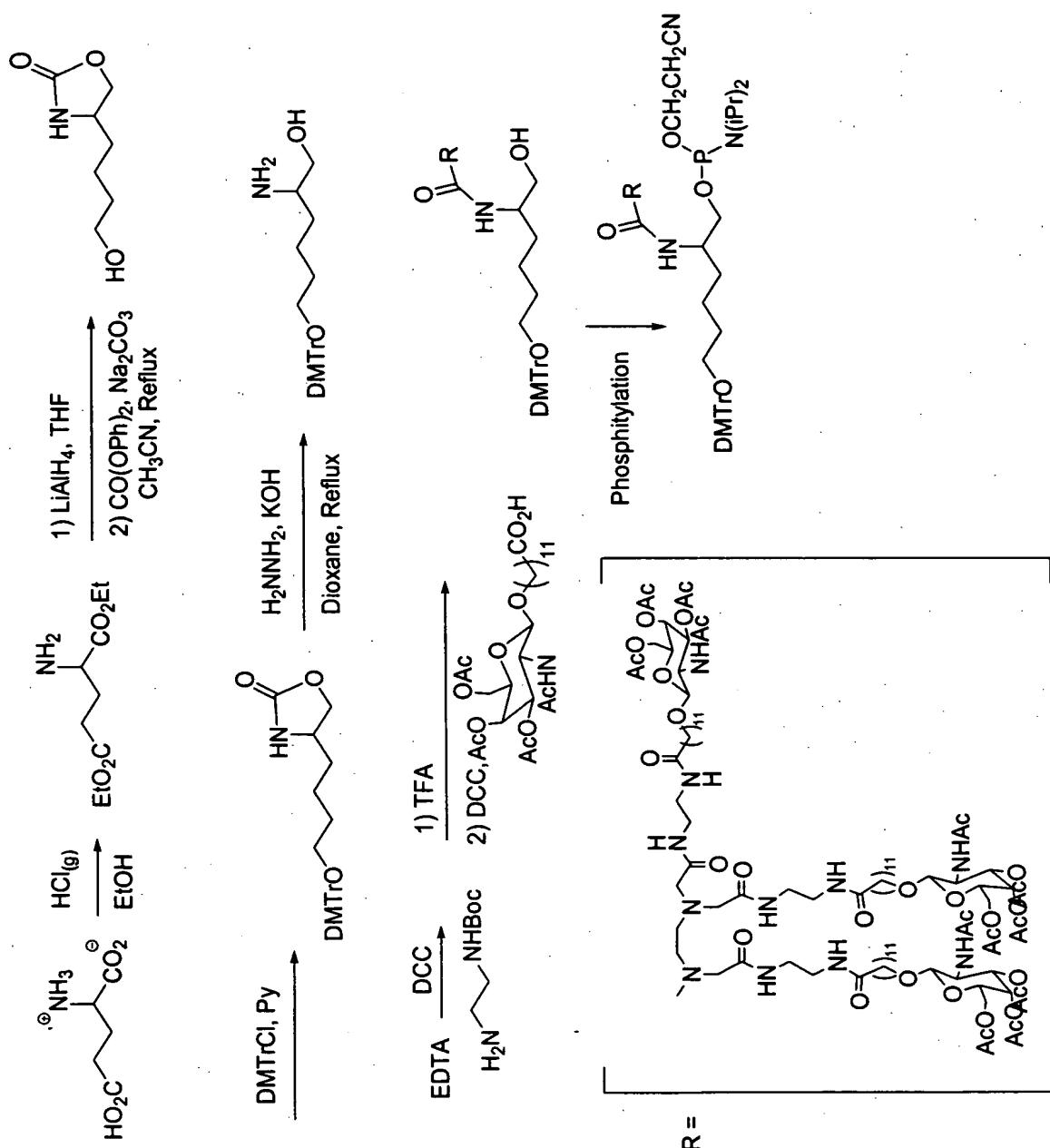
**Figure 46: Synthesis of "tri" Galactosamine phosphoramidite**



**Figure 47:** Synthesis of another Tri-Galactosamine Conjugate



**Figure 48: Alternate Synthesis of Tri-Galactosamine Conjugate**



**Figure 49: Synthesis of NHS Cholesterol Conjugate**

